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The American Journal of Medicine

VOL. VI MAY, 1949 No. 5

SYMPOSIUM ON POLIOMYELITIS

A symposium on poliomyelitis designed for a general medical audience is particularly appropriate at this time because (1) the incidence of the disease has been unusually high in recent years, (2) the percentage of involvement of adolescents and young adults has increased so that the disease is no longer an almost exclusively pediatric problem, (3) significant advances have recently been made on varied fronts of investigation.

Dr. Paul has painstakingly organized this symposium. Some of the most competent and experienced workers in the field have participated. Their presentations deserve careful study.

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routine for discovery

The national total of undiagnosed or "unknown" diabetics may run from a million to two or even three.[1,2] Modern treatment, when promptly initiated, can do much to prevent metabolic decompensation and to minimize diabetic complications. Therefore, the clinical revealment of diabetes mellitus at an early stage is essential.

Thus, "all patients who present themselves to the physician for an examination should have a routine urine examination."[3] In this phase of practice, the advantages of *Clinitest*® tablets for urine-sugar analysis are considerable.

Clinitest is dependably accurate, yet it takes only a few seconds to perform. The test is simple—no external heat need be applied; interpretation is by direct color comparison. *Clinitest* is convenient both for the doctor's office routine and for the diabetic patient's prescribed sugar-level checkups.

(1) Joslin, E. P.: Postgraduate Med. 4:302 (Oct.) 1948. (2) Kemper, C. F.: Rocky Mountain M. J. 45:1092 (Dec.) 1948. (3) Pollack, H.: New York Med. 4:15 (Dec. 5) 1948.

Clinitest

for urine-sugar analysis

AMES

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The American Journal of Medicine

VOL. VI MAY, 1949 No. 5

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Clinical Studies

Seminars on Mechanisms of Congestive Failure

Special Feature

Case Report

General Information

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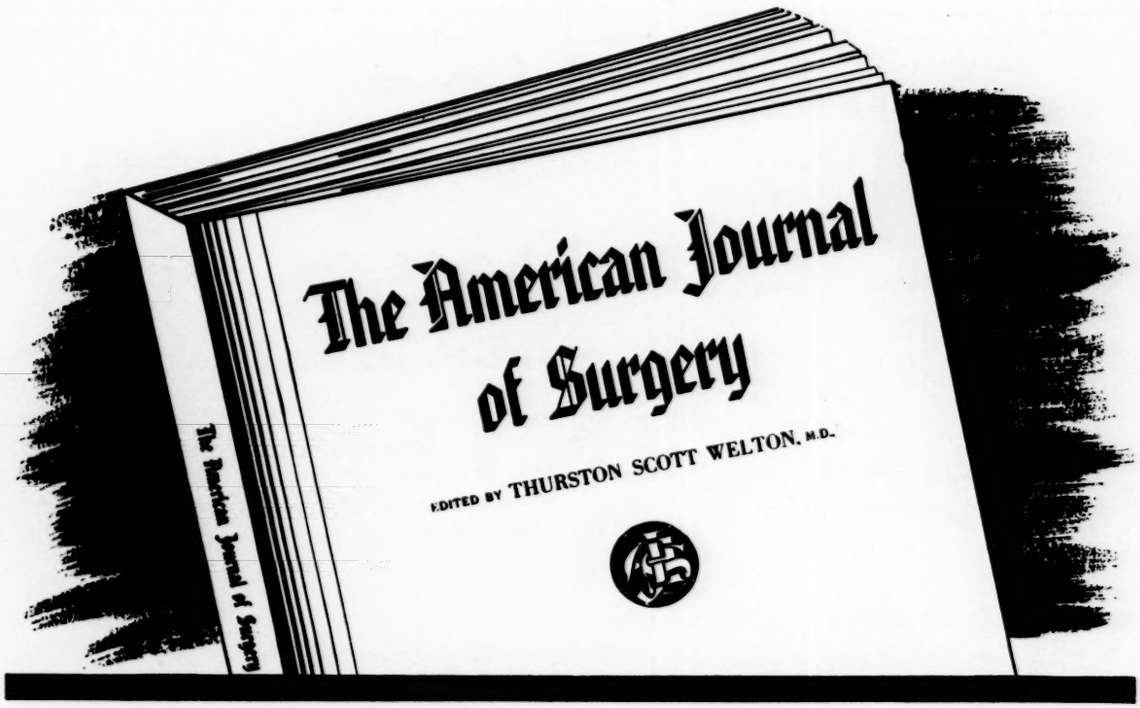

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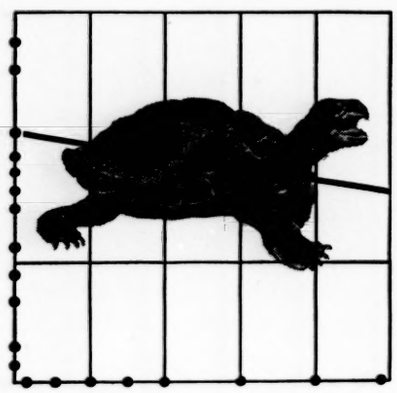

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*Thomas, E. W., et al: *J.A.M.A. 137:1517, 1948*

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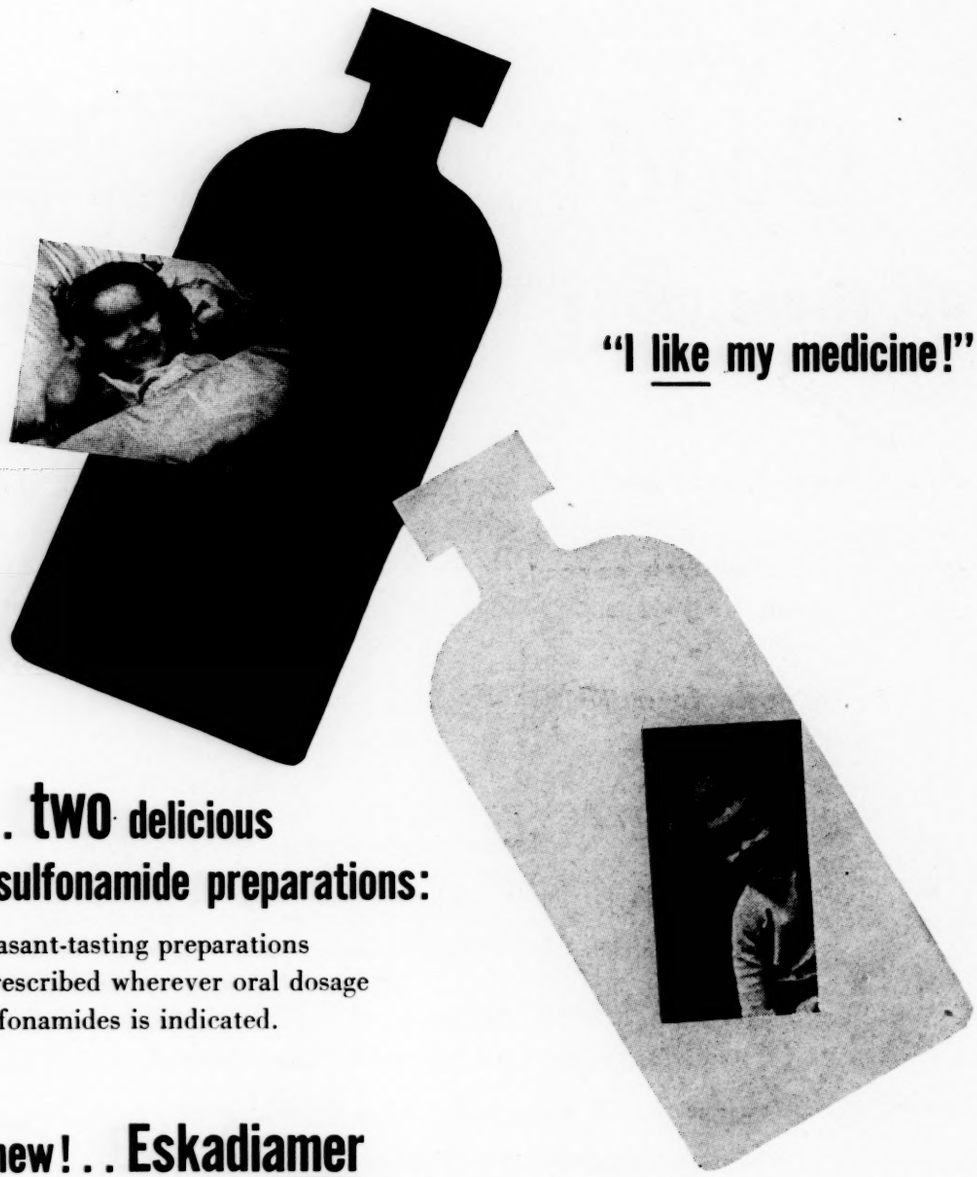

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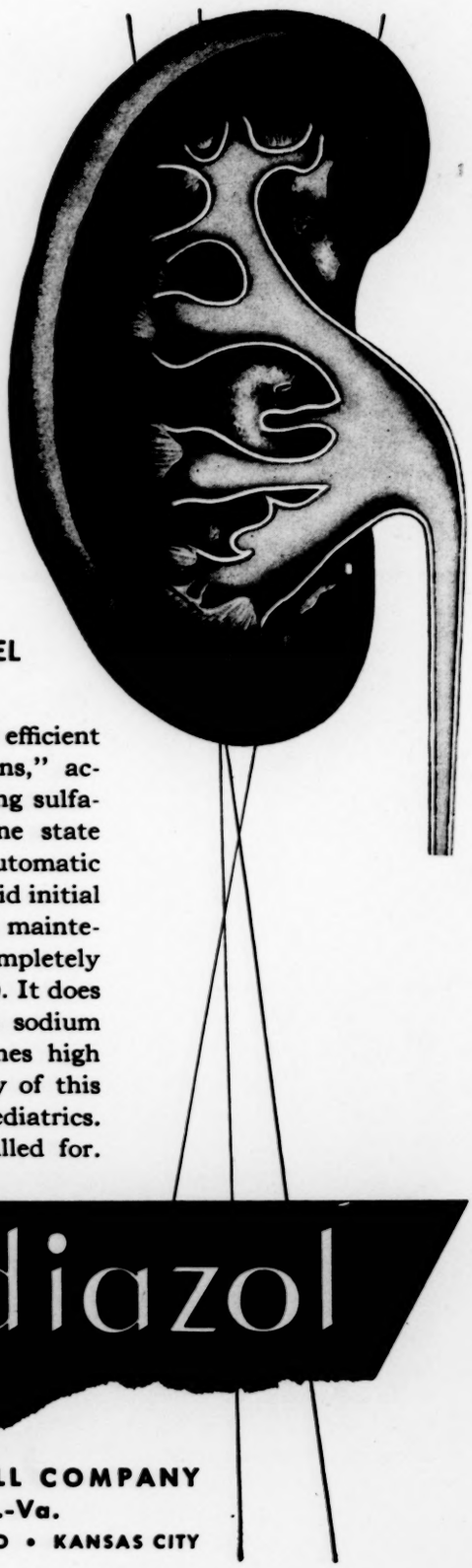

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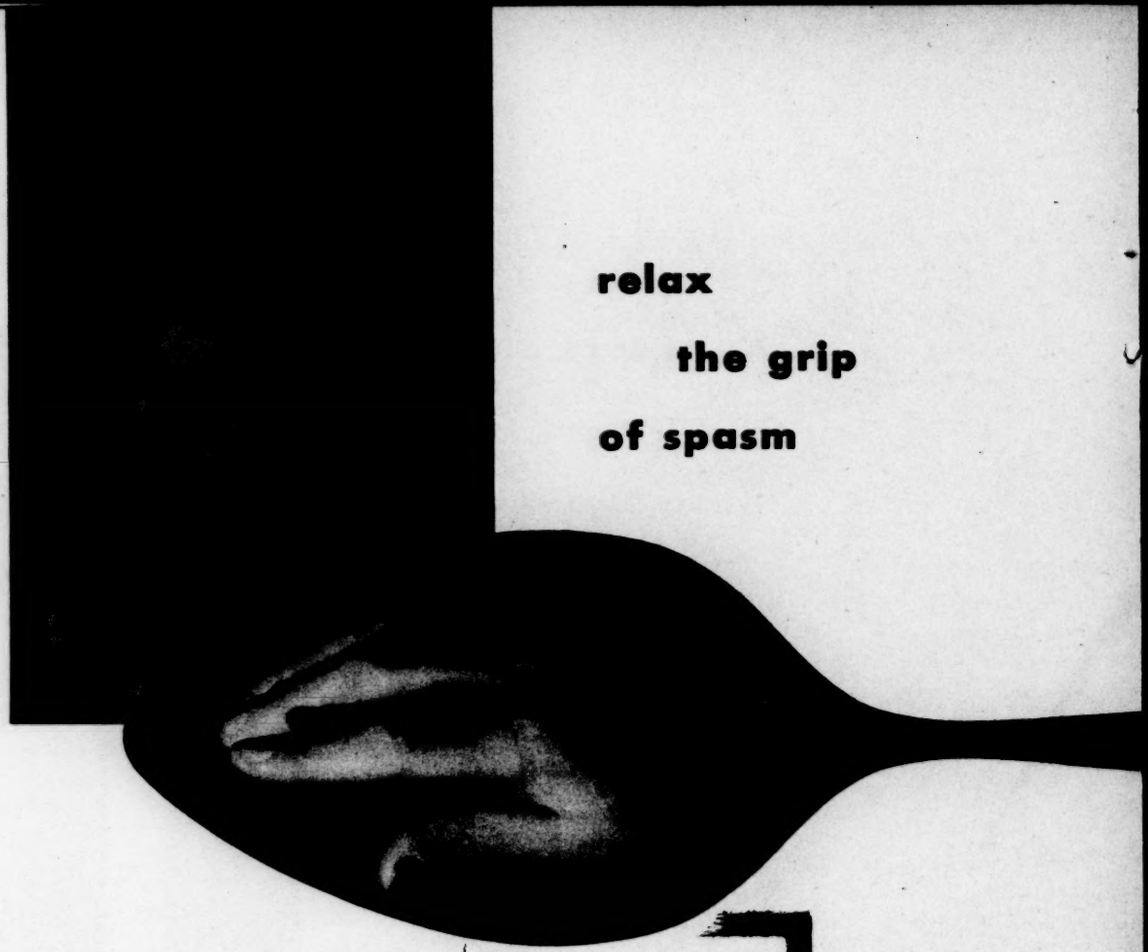

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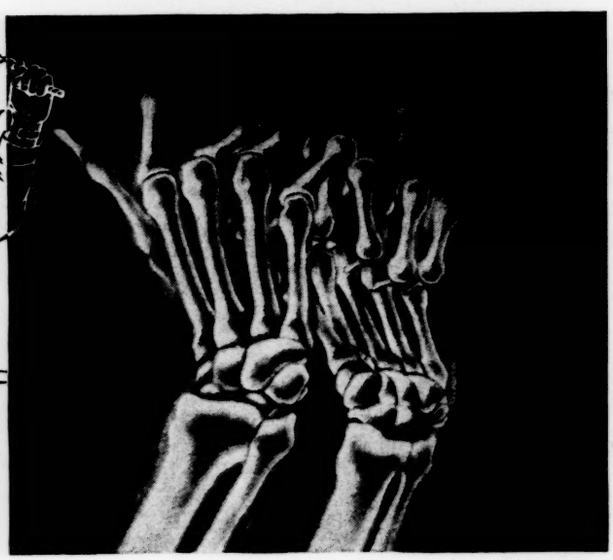

● each capsule contains:

Vitamin D (Irradiated Ergosterol)	50,000 U.S.P. Units
Vitamin A (Fish-Liver Oil)	5,000 U.S.P. Units
Vitamin C (Ascorbic Acid)	75 mg.
Vitamin B_1 (Thiamine Hydrochloride)	3 mg.
Vitamin B_2 (Riboflavin)	2 mg.
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FOR THE ARTHRITIC

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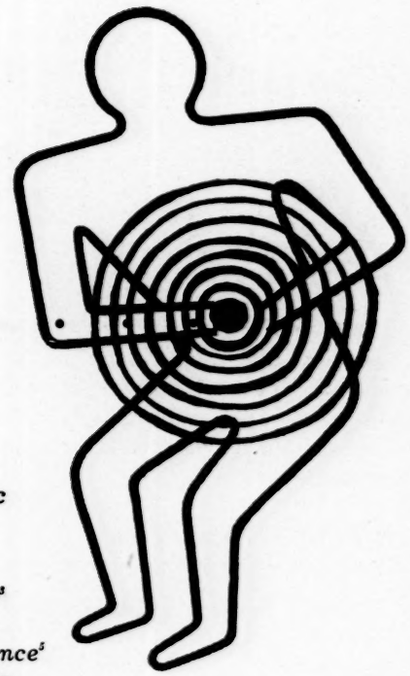

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Potassium not less than	*20.0 mg.*
together with other factors naturally present in dried fresh tomato pulp	*780.0 mg.*

[1] Malyoth, G.: Klin. Wchnschr. *13*:51, 1934.
[2] Bittner, J. E., Jr.: Northwest Med. *35*:445 (Dec.) 1936.
[3] Myers, P. B., and Rouse, A. H.: Am. J. Digest. Dis. *7*:39 (Jan.) 1940.
[4] Powers, J. L.: Bull. National Formulary Committee *9*:5 (Oct.) 1940.
[5] Block, L. H., Tarnowski, A., and Green, B. L.: Am. J. Digest. Dis. *6*:96 (Apr.) 1939.
[6] Morrison, L. M.: Am. J. Digest. Dis. *13*:196 (June) 1946.

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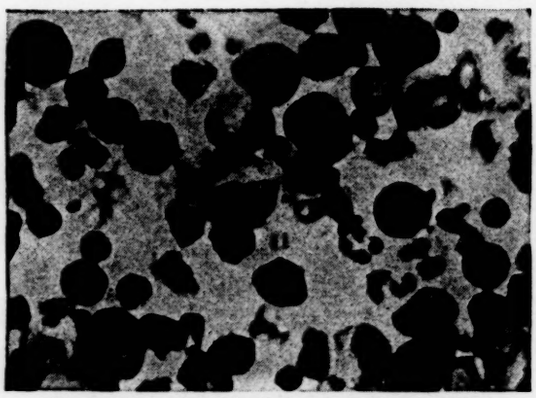
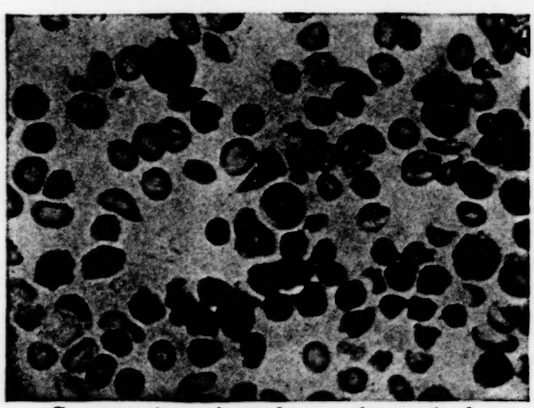


Pernicious anemia before treatment with Cobione (Megaloblastic Bone Marrow)



Same patient ninety hours after a single injection of 0.025 mg. of Cobione

B12

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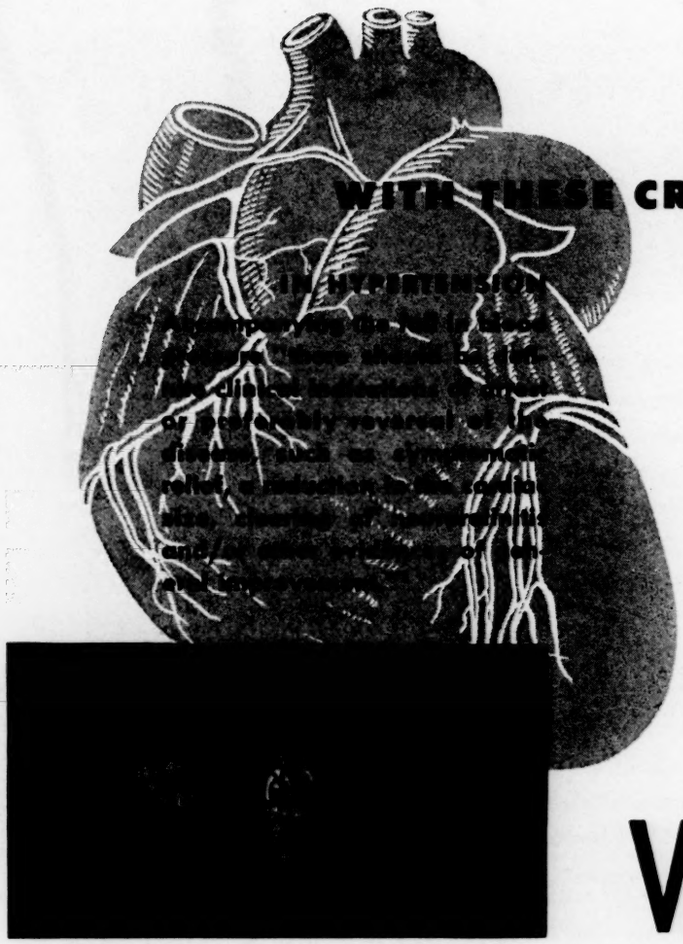

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1. Freis, E. D.: Med. Clin. N. Am. 32:1247-1258, 1948.
2. Freis, E. D., and Stanton, J. R.: Am. Heart J. 36:723-738, 1948.

NOTE: Illustrated brochure on clinical findings, indications and administration of VERTAVIS in severe hypertension sent on request.

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a natural preference

A revealing test[1] recently was conducted on a group of cardiac patients in congestive failure, treated with intramuscular injections of different mercurial diuretics, the identities of which were unknown at the time to both patients and observers. The results showed that the majority clearly evinced a decided—and natural—preference for a diuretic agent that caused the least pain and discomfort—

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BIBLIOGRAPHY: (1) Modell, W.; Gold, H., and Clarke, D. A.: J. Pharmacol. & Exper. Therap. **84**:284, 1945. (2) Gold, H., and others: Am. J. Med. **3**:665, 1947. (3) New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1947, p. 298. (4) Finkelstein, M. B., and Smyth, C. J.: J. Mich. State M. Soc. **45**:1618, 1946. (5) Reaser, P. B., and Burch, G. E.: Proc. Soc. Exper. Biol. & Med. **63**:543, 1946. (6) Griggs, D. E., and Johns, V. J.: Influence of mercurial diuretics on sodium excretion, to be published.

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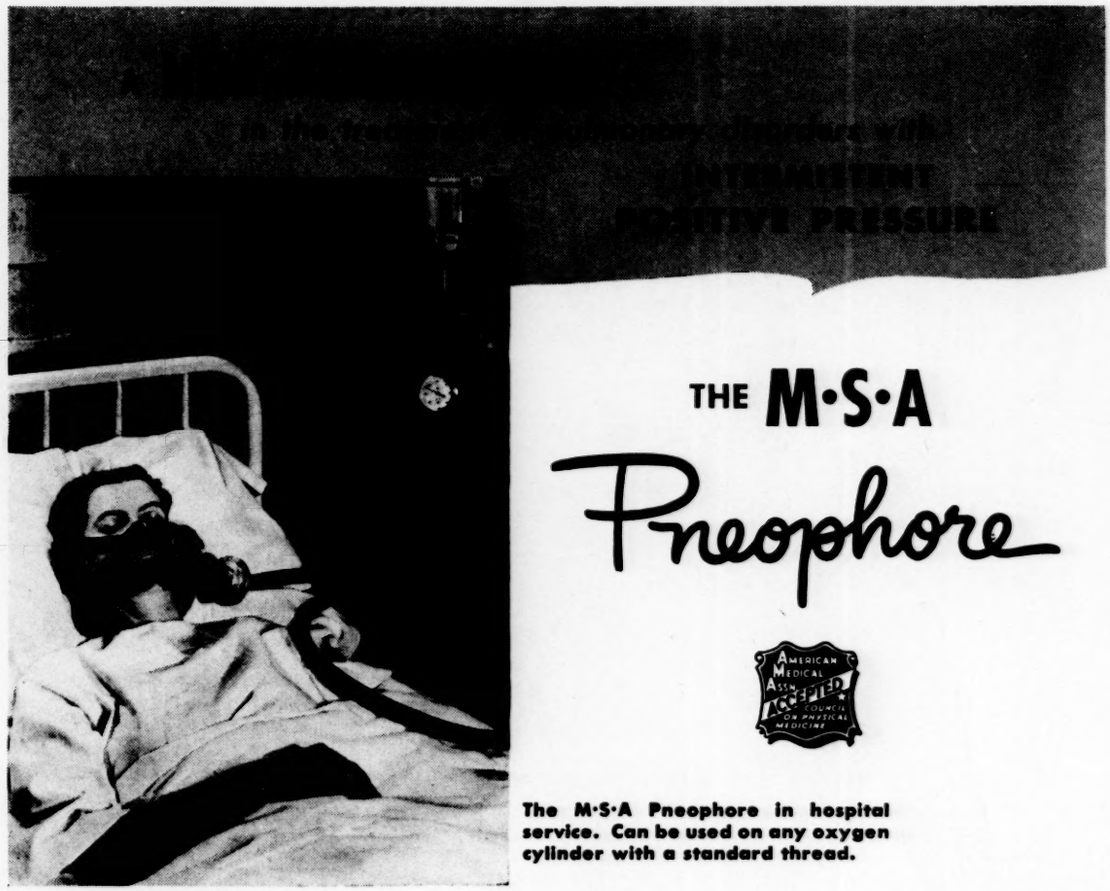

THE M·S·A Pneophore

The M·S·A Pneophore in hospital service. Can be used on any oxygen cylinder with a standard thread.

THE M.S.A. Pneophore is a new, highly effective instrument utilizing intermittent positive pressure to restore breathing in asphyxia.

Among its uses are included (1) emergency care of polio cases with respiratory arrest, until patient can be placed in Drinker respirator; (2) restoration of breathing in apneic patients; (3) aid for victims of inhalation of chlorine, fluorine, and other irritant chemical gases, and (4) a therapeutic measure in conjunction with aerosol distribution of penicillin, streptomycin, or presor drugs—involving cases suffering from asthma, anthrasilicosis and other bronchial disorders.

The differential pressure valve employed by the Pneophore follows the natural breathing pattern of the patient. It cycles rapidly in case of blocked airway, providing audible warning to the operator.

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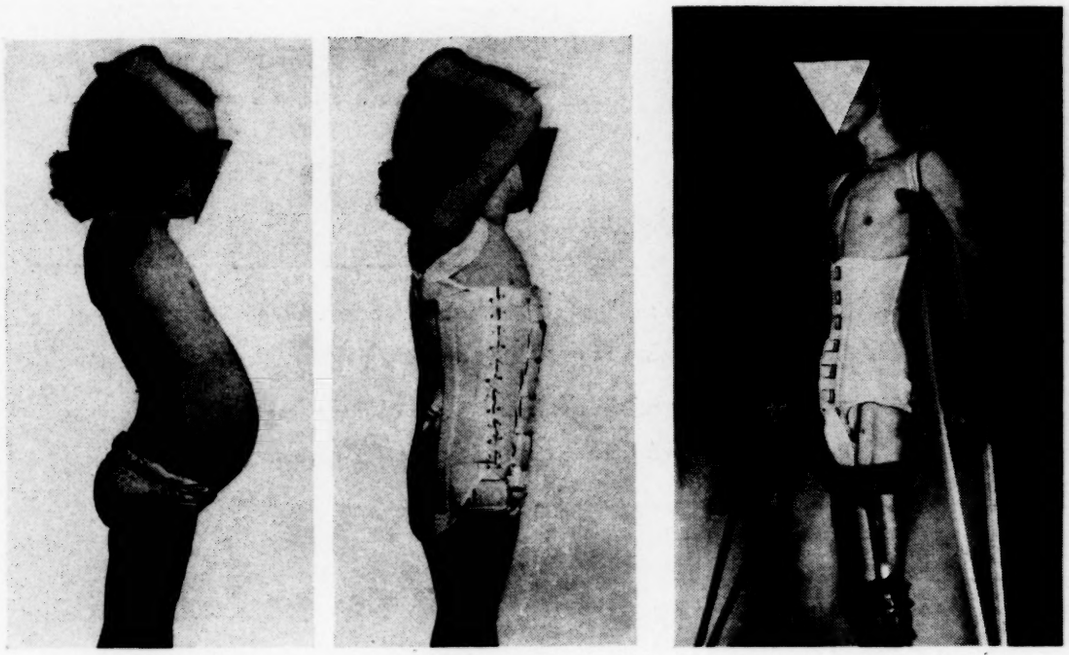
MINE SAFETY APPLIANCES CO.



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There is evidence* to indicate the use of corset-type support in management of convalescent and chronic polio, especially where there is involvement of trunk and abdominal muscles. The patients pictured above are typical examples.

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* *McCarroll, H. R., Treatment of Poliomyelitis in the Recovery and Residual Phases, J. Missouri M. A., 44: 888-893 (Dec.) 1947.*

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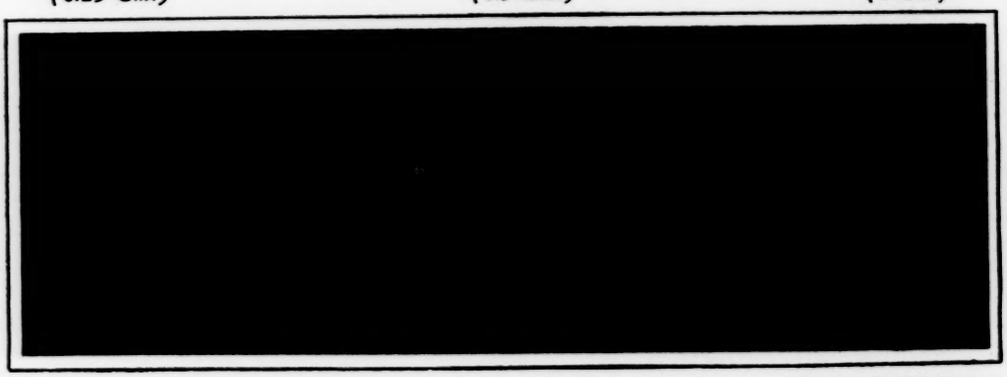

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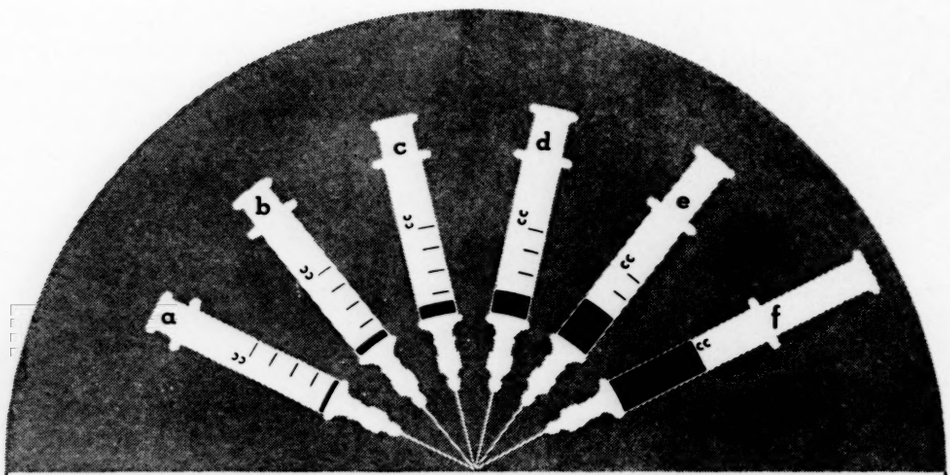

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The American Journal of Medicine

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Foreword

THERE have been many and various symposia on poliomyelitis and perhaps there is nothing unique about this one which might serve to distinguish it from those which have gone before. However, there are points about this series of articles which it would be a mistake not to mention. Primarily they have been prepared for the *internist*, whether he or she is in general practice, special practice or engaged in "hospital medicine." This is the main objective; and if this series of articles can be said to have a central theme, it is the *medical aspect of the acute disease*—the virus infection of poliomyelitis. To supplement this central theme we have tried to include what precedes the acute disease and what follows it in relation to the natural history of poliomyelitis. For, no true clinical description of acute poliomyelitis, however concise, would be adequate today without ancillary considerations with regard to the epidemiology of the disease, its pathogenesis and pathology, its disturbances in physiology, its late management and at least brief mention of its public health aspects.

Some critics might inquire at the onset whether any new series of articles on poliomyelitis is worth reading in view of the claim that so much is written about poliomyelitis and there is so little that is new. With this latter assumption the articles in this symposium take issue. It is true that fundamental questions still remain to be answered, such as (1) How can acute poliomyelitis be cured or arrested? (2) How is poliomyelitis spread? (3) How can poliomyelitis be prevented? But the same can be said of cancer, or certain forms of heart disease and, in fact, many common and important medical conditions. It is freely granted therefore that the answers to these three questions will not be found in these articles but other things will be found both timely and new, and some of these I would like to point out:

For instance, in developing current knowledge of the clinical picture of poliomyelitis Dr. Horstmann has emphasized that textbook descriptions of this disease have in the past been largely limited to the picture of the paralytic disease in infants. Recently there has been a relative shift in the age prevalence of poliomyelitis in this country and Europe and, although all are not agreed as to whether age-specific rates have changed, there is no question that in the average series of poliomyelitis patients which are now seen each summer in this country there is a greater percentage of cases among adolescents and young adults than there was a generation ago, a point which has also been made by Dr. Howe in his article on the epidemiology of this disease. Poliomyelitis in the adolescent or young adult has come to occupy a more important place than ever before. The pediatrician no longer dominates the field. Dr. Horstmann's current studies, based on the large epidemics of 1948 in North Carolina and California, indicate the manner in which adult poliomyelitis differs from old-fashioned "infantile paralysis." Absence of such knowledge in the past has caused confusion and difficulty in the diagnosis of poliomyelitis in adults.

Also, in developing current knowledge of the clinical picture of poliomyelitis Dr. Horstmann has indicated that the clinician cannot pass lightly over the abortive and non-paralytic cases of poliomyelitis even though their significance is trivial as far as a serious result to the patient is concerned. The line which separates the non-paralytic from the paralytic patient is very fine indeed. Thus an important responsibility on the part of the clinician is to protect non-paralytic patients from anything which may upset that delicate balance which determines whether or not the degree of central nervous system involvement will be sufficient to cause clinical paralysis.

Another feature is Dr. Baker's consideration of the most serious clinical form of poliomyelitis, namely, the bulbar form. Within the last three years, management of this type of case has been almost revolutionized.

The after-care of poliomyelitis and considerations with regard to physiotherapy and physical medicine, as well as the approach of the orthopedic surgeon, receives fewer pages in this series of articles than in other similar symposia. We could not cover all fields *in extenso*, particularly as we are concerned here with medical aspects of the *acute* disease. But the orthopedic approach and the technics of physical medicine have not been neglected, to which the articles on the use of moist heat by Dr. Green and the considerations of after-care by Dr. Bennett bear witness.

Some familiarity with the virus of poliomyelitis and its capacity to immunize is essential to the clinician. The lag in this knowledge has been due, in part, to a general lack of appreciation of the fact that there are multiple strains of poliomyelitis virus. Today it is common knowledge that a small but definite family of poliomyelitis viruses exists, as indicated by Dr. Ward. Advances along these lines have been made in Dr. Isabel Morgan's laboratory, and in her article she has mentioned that repeated experimental infections with heterologous strains can be produced in the same animal. It is likely that this also occurs in man for second attacks of poliomyelitis in man might be due to re-infection with different strains of the virus. It would seem that if we are to project these findings forward with an eventual view to possible control of the human disease, the best chance for artificial immunization rests upon an appreciation that the immunizing agent or agents should perhaps be "polyvalent," or at least should have a broad antigenic component.

Another aspect with regard to pathogenesis or pathology is the concept of cerebral lesions in this disease, as developed by Dr. Bodian. The fact that the central nervous system lesions are so extensive, and not limited to the anterior horn cells of the spinal cord, raises considerations as to whether some of the symptoms which have been interpreted by clinicians in the past on the basis of anterior horn cell lesions are not actually due to brain stem or cerebral lesions. Dr. Bodian indicates that as far as the pathologist is concerned all cases of poliomyelitis are 'encephalitic.'

And finally it is a pleasure to have this series as a medium in which Dr. Buchtal of Copenhagen, Denmark again can present the distinguished work of his Neurophysiological Institute to American readers.

John R. Paul, M.D.
Yale University School
of Medicine

Symposium on Poliomyelitis

Epidemiology of Poliomyelitis in the Light of Modern Research*

HOWARD A. HOWE, M.D.
Baltimore, Maryland

ALTHOUGH poliomyelitis was first described by Heine in 1840,[1] it apparently was not recognized as an epidemic disease until much later in the century. The first sizable outbreak to be noted took place in Stockholm in 1887 and comprised forty-four cases. (Medin 1891.)[2] The many reports of scattered cases during this hiatus show with little doubt, however, that the disease was constantly present in western Europe. A similar trend can also be seen in the United States. Colmer in 1843[3] described "teething paralysis," a malady which he found confined to a small group of children under two years of age in Louisiana. This was followed in 1894 by Caverly's account of an epidemic comprising 132 cases of undoubted poliomyelitis in Vermont.[4] In Sweden the year 1905 marked the first of a series of large epidemics of poliomyelitis which were to plague the people of the temperate zones from that time to the present. Wickman's description[5] of this Swedish epidemic (1,031 cases) established the epidemiologic pattern of poliomyelitis and thinking about it has varied little since that time although additional documentation has been produced to support numerous points which were deduced by Wickman on epidemiologic evidence alone.

Wickman characterized poliomyelitis as an epidemic infectious disease affecting children primarily and spread by contact with clinical and subclinical cases or symptomless carriers. He was able to describe many secondary cases apparently resulting from contact with infected individuals, in all probability because the epidemic involved small villages and rural areas which could be intensively studied. This experience has been duplicated in more recent times in other areas, both rural[6,7] and urban.[8,9] The precise type of contact was not known to Wickman nor is it known today.

In 1912 Kling, Petterson, Wernstedt and Josefson[10] found virus in throat washings and intestinal contents from fatal paralytic and non-paralytic patients. While somewhat questionable from a laboratory standpoint, these findings have been amply confirmed in more recent times.[11–16] The discovery of a dual mechanism by which virus might escape from the infected individual unfortunately could not settle the question of the mode of transmission of poliomyelitis nor has the more recent finding of virus in association with flies and urban sewage[17–19] contributed crucial evidence. For some years these basic observations have been shuffled in different proportions into various combinations, some with modern trimmings and with changing emphasis on the means by which virus may reach the susceptible human host. This may never be exactly demonstrated. Nevertheless, recent research has done much to indicate what must be known about poliomyelitis in order to break the chain of transmission at its most accessible point.

Wickman believed that his evidence implicated man as the source of the virus and modern work has done little to refute

* From The Poliomyelitis Research Center, Department of Epidemiology, Johns Hopkins University, Baltimore, Md. Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

this conclusion. No true animal or plant reservoir has yet been demonstrated[20] since even the virus, which is found in association with flies, appears to be of human origin rather than the result of growth within the insect itself.[21] Such being the case, it is logical to look within man's rather immediate environment for the conditions which allow an equilibrium between the host and the parasite. It is therefore necessary to think not only in terms of the degree of man's exposure to the virus but also his reaction to previous exposure, that is, his immunity.

It can be shown in a number of ways that humans become solidly immune to paralysis by poliomyelitis virus although this statement requires some qualification in relation to different virus types which will be made later in this paper. Furthermore, monkeys paralyzed by inoculation of poliomyelitis virus do not become paralyzed again upon re-inoculation of the same material,[22] nor would poliomyelitis continue to be a children's disease except under very special conditions of exposure unless the presence of widespread immunity were the explanation. Thus while the apparent predilection of the disease for children has several interpretations only one seems in conformity with the facts. It is not logical to assume that exposure to the virus is significantly greater in the younger age groups since all ages live in the same homes. Neither can it be shown that mere physiologic maturity brings a type of non-specific resistance for the average age of paralytic patients has been consistently higher in rural areas than in large cities of the same climatic zone.[23–25] The exclusion of these possibilities leaves the acquisition of specific immunity as the most acceptable explanation of the age selection in poliomyelitis. This is corroborated by the fact that the acquisition of serum antibody against the Lansing type of poliomyelitis virus closely follows the age pattern of the paralytic disease[26–28] and that the distribution of antibody to an unclassified virus type in urban and rural areas is also in conformity with the age distribution of the overt disease.[29]

It is generally recognized that many poliomyelitic infections produce no symptoms at all, or that they may be associated with a non-specific syndrome consisting of fever, malaise, headache, nausea, vomiting, constipation or sore throat in various combinations.[30] These cannot with assurance be recognized as poliomyelitic infections even in the presence of an epidemic setting without virus isolation. Patients who present muscle pains and stiff neck or back in addition to the previously mentioned signs and symptoms, and who also show an increase in leukocytes and protein in the spinal fluid as an indication of CNS involvement, may be diagnosed as having non-paralytic poliomyelitis with more assurance, particularly if these symptoms occur in association with paralysis. However, the distinction of these non-paralytic patients from those showing weakness and paralysis of voluntary muscle is entirely one of degree since in both types the CNS is invaded.[31]

One can get some idea of the relative numbers of clinically recognizable and subclinical cases by a comparison of poliomyelitis and measles, diseases which, for the most part, reach the individual before the twenty-fifth year of life. In Baltimore between 1921 and 1944, 119,432 cases of measles were reported among the white population while during the same period only 898 cases of paralytic poliomyelitis were recorded. (Table 1.) Similarly, in the rest of the state of Maryland, exclusive of Baltimore, from 1920–1945 the records show 97,909 cases of measles in all races and 1,185 cases of paralytic poliomyelitis with virtually the same age distribution. It is difficult to escape the conclusion that there were during this period an average of one hundred poliomyelitic infections to one reported case.

Approximately the same ratio of clinical to subclinical cases is indicated by the survey of Selwyn Collins[32] which included 20,258 individuals from zero to twenty-four

years of age in twenty-eight cities of the United States. In this group 11.01 per 1,000 had a history of antecedent poliomyelitis, including death. Since poliomyelitis incidence is negligible over twenty-five years of age, these figures indicate that effective immunity had been achieved by the population at the rate of approximately one hundred infections to one clinically recognized case. A similar ratio has also been arrived at by Casey and his co-workers on the basis of clinical-epidemiologic observations.[33]

TABLE I
REPORTED CASES OF MEASLES AND POLIOMYELITIS BY AGE GROUPS—COUNTIES OF MARYLAND, 1916–1943

Age Groups	Cases of Measles			Cases of Poliomyelitis		
	As Reported	Accumulated by Age		As Reported	Accumulated by Age	
		No.	Per Cent		No.	Per Cent
0–4	24,128	.....	24.3	614	.....	51.7
5–9	43,087	67,215	67.8	282	896	75.6
10–14	16,365	83,580	84.3	157	1,053	88.9
15–19	6,772	90,352	91.2	69	1,122	94.7
20–39	7,109	97,461	98.4	53	1,175	99.1
40–59	708	98,169	99.1	5	1,180	99.6
60+	95	98,264	99.2			
Unknown	815	.....	0.7	5	.....	0.4
Total:	99,079	99,079	100.0	1,185	1,185	100.0

*Figures obtained through the courtesy of Dr. Riley of the Maryland State Dept. of Health.

Another picture of the subclinical immunization process may be seen by comparing the reported cases of poliomyelitis over a period of twenty-five years in a large city such as Baltimore with two smaller cities of Maryland. (Table II.) While the disease has been reported every year in Baltimore with periodic upswings, the smaller cities of Hagerstown and Easton have had a much less spectacular, although typical, experience with poliomyelitis.

In Hagerstown and its rural districts poliomyelitis has been reported only half of the years from 1925 to 1948, inclusive. During that time the largest reported outbreak consisted of eleven cases, producing a "rate" of roughly 37 per 100,000 persons which is equivalent to those reported in Baltimore at epidemic times. Easton and its environs were conscious of poliomyelitis but four times during this twenty-three-year period. In 1941 two cases were reported, producing a rate of 58/100,000. No one can doubt that poliomyelitis was present more frequently and extensively than is indicated by these "epidemics," and that the populations of these towns were being immunized with only slightly less thoroughness than those of Baltimore. The consistent selection of children under twelve years (100 per cent in Easton and 70 per cent in Hagerstown) is the best proof of this.

TABLE II
REPORTED CASES OF POLIOMYELITIS IN MARYLAND

	Baltimore (white patients only). 1940 White Population 693,257	Hagerstown and Rural District. 1940 Population 32,491	Easton and Rural District. 1940 Population 4,528
1925	21*	2†	0†
1926	26	0	0
1927	9	0	0
1928	122	1	0
1929	9	0	0
1930	19	3	1
1931	13	1	0
1932	13	0	0
1933	13	0	0
1934	10	0	0
1935	46	0	0
1936	6	11	0
1937	45	0	0
1938	2	0	0
1939	10	0	1
1940	4	0	0
1941	90	2	2
1942	3	1	0
1943	7	1	0
1944	152	5	0
1945	21	2	0
1946	25	0	0
1947	26	3	1
1948	13	2	0

*Figures from the Baltimore City Health Dept. (courtesy of Dr. Fales).

†Figures from the Maryland State Health Dept. (courtesy of Dr. Riley).

It is important, however, to emphasize that while these estimates probably reflect the over-all picture they may be in error for any given situation. For example, it is generally accepted that certain virus strains consistently produce severe paralysis in laboratory animals while others may be associated with such mild disease that microscopic examination is necessary in many cases to establish the existence of infection. There is every reason to believe that these same differences occur in nature. Since the recognition of a poliomyelitis epidemic depends primarily on the identification of cases, it is clear that a number of variables will determine the extent of its recognition. These include not only the severity of the infection, as has been just suggested, but also the reporting practices and abilities of the attendant physicians, as well as the season and locality in which disease occurs and also the residence and age of the patients. These last variables may account for deficits in reporting as high as 68 per cent, even in a poliomyelitis-conscious community (the state of Massachusetts) where small town physicians are particularly loath to make a diagnosis of poliomyelitis in an infant during the winter months of a non-epidemic year.[34] It is not surprising, therefore, to encounter numerous inconsistencies in the reported incidence of poliomyelitis.

Modern laboratory studies have shown the virus of poliomyelitis to be present in stools during the acute stages of the paralytic disease in such a high percentage of cases that it seems justifiable to consider it a constant concomitant of CNS invasion.[35,36] This probably is true for non-paralytic patients although the documentation is not extensive. Within a week of the onset of symptoms the frequency with which virus can be demonstrated in stools falls off but, nevertheless, virus has been shown to persist in some individuals for as long as eleven to twelve weeks.[13,37,38]

Virus has also been demonstrated in swabs taken from the throats of acute paralytic patients and in face masks worn by juvenile patients who had coughed and drooled into them.[39] While virus has been isolated from the throat[14–16] in nearly 50 per cent of the patients within three to five days of the acute onset of disease, its incidence falls off very rapidly thereafter. Occasional isolations from abortive cases are recorded as late as the eleventh day.[16] It is probable that the failure to detect virus in the oropharynx as long as in the stools reflects a real biologic difference since it is known that antibody may be present in the pharyngeal secretions,[40] although it has not been demonstrated in the stools. It is therefore possible that the antibody response following infection clears the pharynx of virus in a relatively short time.

Little is known about the incidence of virus in the stools or pharyngeal secretions prior to the onset of symptoms although it has been described in the former twelve and nineteen days before onset.[41,42] There have also been a few isolations of virus from the oropharynx four to six days before clinical symptoms were observed.[43,44] Investigation of the virus distribution in the family associates of a patient has amply demonstrated the relative frequency of asymptomatic virus infections of the alimentary tract[45–47] while random sampling of the population at epidemic times has suggested a wide distribution of oropharyngeal and fecal virus carriers[48–50] many of whom were not sick. Pearson et al.,[46] in a survey of infected individuals in the Fort Worth, Texas poliomyelitis epidemic of 1943, have provided the data from which to compare the number of observed subclinical infections with that expected if the ratio of clinical to subclinical infection were approximately 100 to 1. For example, during the period of their study ten cases of reportable poliomyelitis occurred in a city of 200,000 persons. If in reality 1,000 infections had developed during this period, one would have expected an infection rate of .005. The investigators drew a sample of 374 persons who had no known history of contact with a patient with poliomyelitis. On the basis of the aforementioned rate 1.8

silent infections would have been expected in this group and at least two were found.

Modern studies have effectively ruled out the olfactory mucosa as a portal of entry of the virus by the demonstration that the olfactory bulbs of fatal human patients do not show characteristic lesions[51,52] or contain virus.[53] Nor is there evidence that the virus proliferates in the olfactory mucosa[53] although it is easily found in the pharynx and contents of the gut of both patients and carriers. Although it is not entirely clear how the virus gains entrance to the alimentary tract, the evidence points strongly to it as the tissue from which invasion of the CNS takes place. There is a large body of fact indicating that the virus travels by way of nerves to the CNS and is disseminated within it along nerve pathways.[105]

Poliomyelitis might be transmitted from one individual to another in a variety of ways: indirectly by an arthropod vector with or without an animal reservoir, through mass contamination of food or fluid by feces, relatively directly by hand-to-mouth transfer of feces or pharyngeal secretions from child to child or through playthings, finally, by immediate droplet ("respiratory") contact.

The first possibility, that of a blood-sucking arthropod with or without an animal reservoir, may be ruled out with reasonable assurance. Since poliomyelitis does not have an important blood stream phase,[54] there is little reason to expect that blood-sucking insects would become infected from man. Furthermore, it is difficult to visualize either an animal reservoir or an arthropod vector of sufficiently universal distribution to account for the world-wide extent of poliomyelitis. Also, the diffuse pattern of poliomyelitis in city and country is quite different from the rural concentration of St. Louis encephalitis and equine encephalomyelitis, both mosquito-borne, as well as the special localizations of arthropod-transmitted rickettsial disease.[55] Furthermore, the persistence of poliomyelitis epidemics into the winter months clearly differentiates this disease from mosquito-transmitted equine encephalomyelitis which ceases abruptly with the advent of cold weather.[56]

Spinal cord emulsions containing Lansing virus are rapidly inactivated by sludge.[57] Nevertheless, since it is known that active virus is discharged by certain sewage plants into streams, contaminated water is a potential source of infection. While there is some difficulty in translating the results of laboratory experiments to the conditions of urban water disinfection,[58,59] it appears that ordinary methods for the purification of drinking water are effective. Even if this were not true, however, the slow radial spread of poliomyelitis from a circumscribed focus is not that of an explosive epidemic disseminated through a city water distribution system.[7,60] It is impossible to consider drinking water as the agent for dissemination of the disease in rural districts where each family usually has an individual water supply unless one thinks of the entire water table of an area as contaminated.

Mass contamination of a single source of milk has been reasonably indicated in only three epidemics despite diligent search so that it seems likely that mass contamination of food would not go unnoticed.[61–63] The fact that there are frequently multiple cases occurring in families within a few days suggests a common exposure. Lavinder, Freeman and Frost[60] found 70 per cent of multiple familial poliomyelitis cases occurring within five days and but 40 per cent of diphtheria or scarlet fever cases so distributed. Aycock and Eaton[64] suggested that this phenomenon could be explained by the advent of an asymptomic carrier into a household. However, it is also consistent with the idea of contamination of food by flies.

In a very ingenious experiment Ward, Melnick and Horstmann[65] exposed bananas and fly bait to flies for twenty-four to forty-eight hours on the back porches of some twenty rural homes in which there was poliomyelitis. When the material was fed to two chimpanzees, both developed inapparent poliomyelitic infections. Unfortu-

nately, the food was to some extent also exposed to the general environment as well as to the flies so that this important control is not entirely satisfactory, but there seems to be little reason to doubt that a large number of infected flies could contaminate food if allowed access to it for considerable time.

It is difficult to assess the role of flies in the usual spread of infection. Experiments on fly abatement with D.D.T. have not resulted in any demonstrable control of epidemics but have almost invariably been instituted while the epidemic was at its peak or on the decline.[66]

Another episode which appears to minimize the importance of flies took place in connection with an unprecedented poliomyelitis outbreak on the Island of Malta where human sewage is used to fertilize the fields. During August and September the incidence of typhoid rose but the outbreak of poliomyelitis did not occur until December and January when there were virtually no flies present.[67] It may also be valuable to cite an outbreak of poliomyelitis at Elkins, West Virginia involving seventy cases which took place entirely in the winter.[68] The temperature was below freezing most of the time and flies were seen only occasionally on unusually warm days.

For the most part, infected flies have been trapped in rural areas where they had ready access to human feces,[69] but infected catches have also been made in cities with modern sewage disposal such as Cleveland, Ohio[70] and Rockford, Illinois.[71] Despite these findings urban fly populations in general have declined greatly since the advent of the automobile, with a concomitant decrease in dysentery rates but without any corresponding decrease in the incidence of poliomyelitis. The role of the fly then remains an indeterminate one since no positive evidence for its participation has been advanced to counter such negative evidence as the aforementioned.

While it was claimed in 1911 that poliomyelitis virus had been isolated from the dust of a sick room,[72] confirmation of this observation with modern methods has not come to light, nor is it known how long virus remains active when dried in fecal remnants or droplet nuclei. While virus might retain its activity for some hours on inanimate objects, it is not necessary to postulate a longer survival time to account for the transmission of the disease.

The evidence for direct person to person transfer of virus is again largely circumstantial. However, no one who has watched children at play can doubt that many opportunities exist for the transfer of pharyngeal secretions or feces, not only among the children themselves but also to their adult associates. Two independent epidemiologic studies based upon secondary cases presumably arising from a single contact with an extrafamilial primary case[6,73] both indicate the infectious period to be four to five days before and after the onset of symptoms. This interval, of course, corresponds very closely to that during which virus is readily demonstrable in the pharyngeal secretions of the patient. The fact that the continued elimination of virus in the stools has not been connected with appearance of secondary cases again constitutes negative evidence in favor of spread through pharyngeal secretions. Both poliomyelitis and measles spread radially and appear to be equally infectious[7,74] yet patients with poliomyelitis do not have the cough or coryza which is characteristic of measles. It must be recognized, however, that some children emit visible mouth spray even in ordinary conversation. Since the minimal infective dose of virus probably is very small and the virus might at some times be present in saliva, this type of direct contact is at least possible. It has received little attention by modern workers. The absence of lesions in the olfactory bulbs of man does not necessarily rule out airborne infection. This simply may be an expression of the experimentally observed fact that the nasal mucosa is not a tissue in which the virus proliferates as readily as in the oropharynx.

Since the carrier state may be transient,

the demonstration of infection in all the members of a family at the time of its occurrence[15,45–47] does not prove that all of the individuals were infected by a common exposure unless it can be shown that all were free of virus on more than one occasion during a period of five to twenty-one days previous to the onset of the disease.

Although it appears that much of the evidence favors the idea that poliomyelitis is transmitted through pharyngeal secretions, the suggestive power of analogy is so strong that it is very difficult to avoid falling in with the idea that a disease with a summer epidemicity is invariably enteric. The possibility still exists that there is a dual mechanism involved and that fecal contamination, both through the agency of flies or by more direct transfers, may operate under certain conditions. This point of view recently has been presented and ably supported by Sabin.[75] It has been suggested, furthermore, that flies may be responsible for the initiation of summer outbreaks which then continue by person to person contact.[65]

While poliomyelitis was recognized as an epidemic disease in the north temperate zone just before the turn of the century, it is still essentially endemic in character in such places as Malta,[67] El Salvador,[76] Puerto Rico,[77] Venezuela,[78] Ecuador[79] and Palestine[80] where, with the exception of Malta, only small outbreaks have been noted in recent years. In these epidemics, as in the first ones to be recorded in north Europe and the United States, 80 to 90 per cent of the cases occurred in children under five years of age. While doubtless only the severe paralytic cases have been recognized, the remarkable correspondence of age selection in all of these areas can scarcely be laid to ignorance of paralytic poliomyelitis in older children or in adults. It seems probable that lack of recognition of the disease would create less distortion in the pattern of age selection than in that of total incidence. It is certainly difficult to explain the apparent absence of large epidemics in relatively primitive countries on the basis of the continued presence of mild virus strains since during World War II British and American troops contracted paralytic and even fatal disease while stationed in areas where poliomyelitis was virtually unknown in the native populations.[67,81–83] Obviously, then, one can say relatively little about the character of poliomyelitis in primitive countries beyond noting that the disease is clearly world-wide in its distribution.

TABLE III

AGE SPECIFIC MORBIDITY RATES—ADJUSTED TO TOTAL RATE FOR 1920-1924 (MODIFIED FROM DAUER)

Year	Age Groups				Factor
	0–4	5–9	10–19	20+	
1920–24	32.5*	14.9	7.9	1.4	1.000
1925–29	22.6	15.1	6.4	0.80	0.6715
1930–34	22.6	20.3	7.8	0.81	0.4517
1935–39	20.6	23.3	9.1	0.76	0.7582
1940–44	14.9	22.4	9.5	0.93	0.5476

AGE SPECIFIC POLIOMYELITIS MORTALITY RATES—ADJUSTED TO TOTAL RATE FOR 1920–1924

1920–24	5.3*	2.7	1.6	0.34	1.000
1925–29	3.9	3.1	1.9	0.34	0.9041
1930–34	3.6	3.9	2.3	0.47	1.0645
1935–39	3.6	4.1	2.5	0.64	2.2758
1940–44	1.4	3.8	3.0	0.64	2.000

* Average annual rates per 100,000 persons.

Since the recognition of poliomyelitis as an epidemic disease, further modifications in age selection have taken place which in all probability reflect both the past and present experience of the population with the virus. For example, in the United States there has been a consistent reduction in the age specific rates for children under five years. This has been noted in relation to deaths since 1910 for the registration area of that time by Gilliam,[84] and since 1920 in relation to total reported cases as well as deaths in five northern states by Dauer[85] whose figures are presented in Table III and Fig. 1. Both authors agree that there has been a progressive decrease in total death rates although considerable variability is encountered from year to year because of local factors. In order to empha-

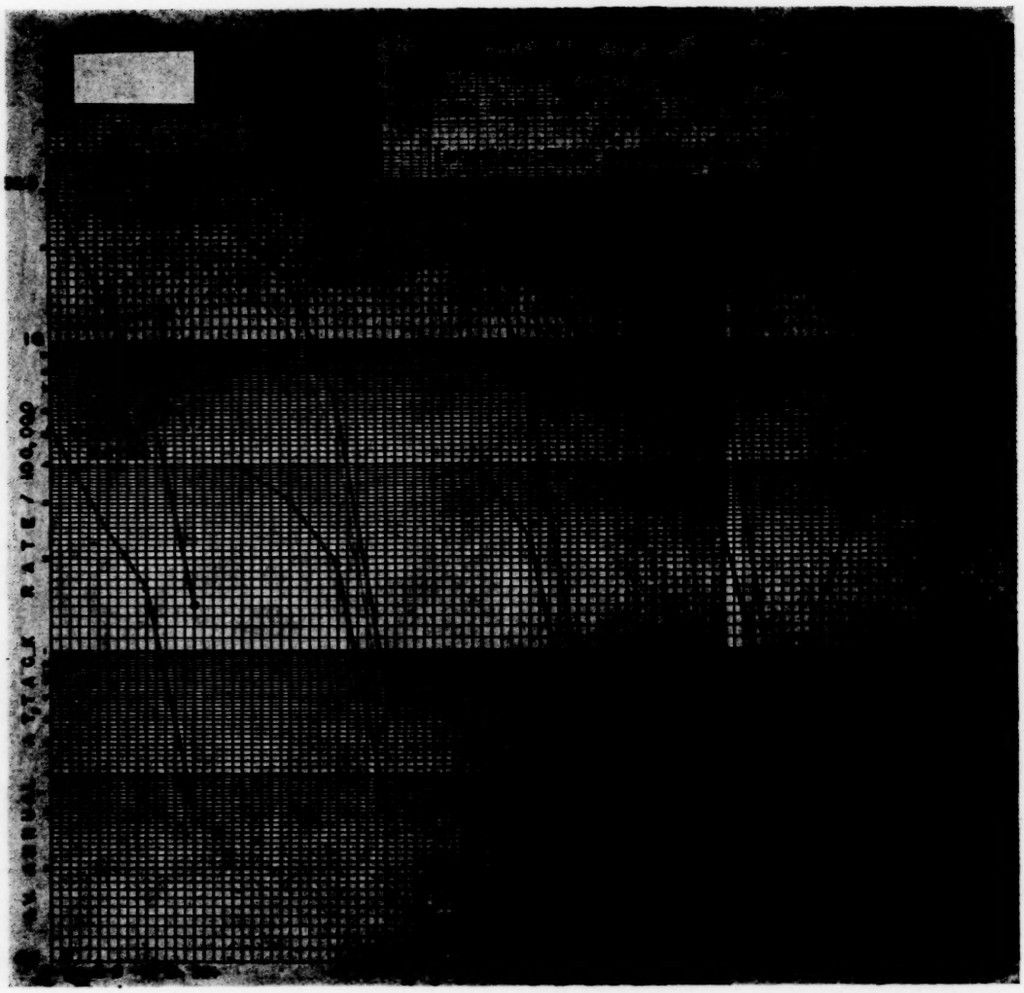

FIG. 1

size the age trends the average five-year rates for the age groups have been multiplied by a factor representing the relative decrease or increase in the total rate since 1920 to 1924 (last column in Table III). When this is done, the relative shifts in age selection are clearly visualized. It can be seen that the striking decrease in deaths under five years has apparently been balanced by a rather uniformly distributed increase in all the older groups.

Total reported cases (paralytic and non-paralytic) show the same trends although the relative drop in the rates under five years is less spectacular than that observed in the death rates. Here there has been a definitely greater incidence in the five to nine-year group so that the slope of the first limb of the curve has changed because of alterations at both ends. While there is a slight relative increase in the ten to nineteen-year class, this limb of the curve has scarcely altered its slope, indicating that changes in this group relative to the five to nine-year group have been proportional. Such a small increase has taken place in the selection of adults that there is scarcely any perceptible alteration in the slope of this portion of the curve.

Essentially the same findings have been reported since 1911 for Denmark and Sweden[86,87] where deaths and paralytic cases have been tabulated separately, thus avoiding admixture of an unknown number of non-paralytic patients who do not have the same age distribution as the paralytic

ones.[87–89] In the Scandinavian countries there has been the same relative reduction of incidence under five years of age but a considerably more marked selection of adults than is indicated by the American statistics. The shift toward older ages, however, is by no means as striking as one is led to believe from tabulations dealing only with the per cent age distribution of patients, a measure which is distorted by the marked aging of the population.

It is impossible on the basis of present knowledge to do more than suggest several possible explanations for this phenomenon. Burnet[90] has advanced the hypothesis that mutation of the virus has resulted in strains which produce a higher percentage of paralytic infections. While mutation of the Lansing type has been known to take place under drastic experimental conditions, there is thus far no crucial evidence that this has happened in nature nor is it clear that the actual incidence of paralytic disease has greatly increased. Dauer[85] suggests that much of the apparent trend in the last twenty years may be due to improved criteria for diagnosis and more complete reporting.

The decrease in the size of families must also be considered in this connection. If the virus is introduced into the family by older children, it is obvious that a child without older siblings has less opportunity of meeting the virus in infancy than the child who is a young member of a large family. In this case, however, one would expect a shift in the age incidence of other childhood diseases. The experience of Baltimore in this regard is of interest although it may not be typical. The population has been aging since 1920 and, concomitantly, there has been a shift of maximal paralytic poliomyelitis incidence from the zero to four to the five to nine-year group. At the same time, however, there has been no comparable change for measles and whooping cough. This suggests that the epidemiology of the latter two diseases is different from that of poliomyelitis, also that they have reached a stable equilibrium with the population which is not easily upset while such is not the case for poliomyelitis. (Fig. 2.)

Selwyn Collins' study[32] has shown the age shift to be greater in the group with an income above $3,000. This suggests that the better class home is not so heavily seeded with virus as in the past. This would be equally true whether the virus were introduced by the school age child or whether it had become less prevalent in the home because of reduced exposure of food, etc. to flies or because of other sanitary improvements. In the countries which have shown changes in age selection the past generation has seen marked alteration not only in general sanitation but also an improvement of diet and the degree of housing congestion. These changes, perhaps collectively, have been accompanied by striking reductions in the incidence of enteric diseases such as typhoid and dysentery. Meanwhile, little has happened to poliomyelitis beyond the shift in its age selection which has just been discussed.

The demonstration of at least three immunogenically different types of poliomyelitis virus[91–93] offers the possibility of clarifying considerably the irregularities in epidemic pattern which are encountered from time to time[94] even though there may be considerably more cross immunity following natural infection than has been demonstrated in artifically immunized laboratory animals.[22] It is also of more than passing interest that strains of virus which are immunogenically indistinguishable nevertheless differ markedly as regards their clinical properties in laboratory primates, some being very mild and others producing extensive paralysis.[93,95] The possibility, therefore, exists for a succession or a mixture of types in various times and areas. It may not be irrelevant in this connection that strains representing the three presently known types have all been isolated from the Los Angeles area since 1934. Two of these produce very severe disease in monkeys while the third is very mild.

While it is highly probable that more

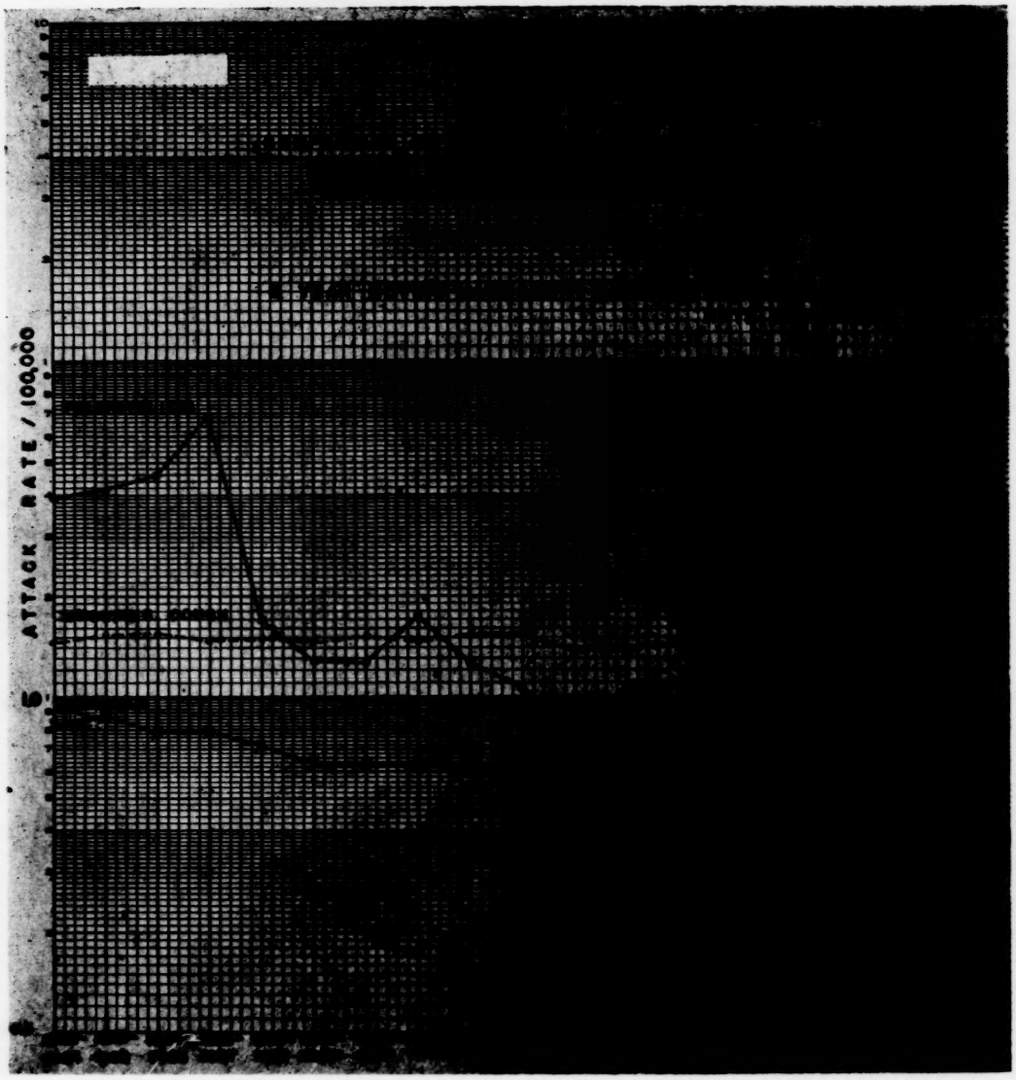

FIG. 2

than three types of virus exist, the number cannot be large else poliomyelitis would not be primarily a children's disease. The fact that well authenticated second attacks of poliomyelitis occur in no way abrogates the interpretation that adult immunity is the result of specific experience with various virus types. Second paralytic attacks may be induced in the laboratory with heterotypic virus types but it is significant that even under these extreme conditions paralytic rates are much lower than those observed in animals which have had no previous experience with poliomyelitis virus.[22] Several studies in recent years[96–98] have purported to show that attack rates for the entire susceptible population in a given epidemic are of the same order of magnitude as those for second attacks. This is interpreted to indicate a complete absence of immunity following the first paralytic attack. Leaving aside the small numbers of second attacks and the questionable procedure of accumulating the paralytic cases over a period of nearly a generation as a denominator for calculating the rate of second attacks, a serious difficulty remains. Paralysis is an exceptional outcome of poliomyelitic infection and is suspected to be a function of genetic constitution.[99,100]

In measuring second paralytic attacks one is therefore measuring a special event in a group already selected by the previous occurrence of this event—the risk of paralysis in a group of persons already shown to be especially susceptible to paralysis. This interpretation was, in fact, suggested by one group which participated in a study of second attacks.[97]

Attempts at the control of poliomyelitis must be based upon a realistic interpretation of its epidemiologic characteristics. Since the ratio of unrecognized to recognized infection is of the order of 100/1, no widespread effect can be expected from the isolation of the patient and his immediate contacts, even though it has been shown that these represent an appreciable number of infected individuals. At best, one could look forward to preventing a few cases of infection (no one would willfully condone association with a patient or his family) but could not expect any appreciable effect upon an entire epidemic. While swimming pools are certainly a potential source of contagion, they have never been clearly implicated in the actual spread of the disease.

It seems inadvisable to hamper the life of an entire community for an objective which cannot be attained and which, if successful, would only delay to a less favorable age[55,101] a natural immunization process which goes on at the rate of one casualty in one hundred infections. While it may be necessary to do something to maintain community morale, the physician who has no illusions regarding the effectiveness of "control measures" can keep them at a minimum. Quarantine has clearly not eliminated epidemics of measles, a disease in which virtually every infected individual and many of his contacts can be identified and eventually isolated.

The logical point at which to break the chain of infections is not by attempting to reduce exposure but rather to control infection by increasing immunity. While vaccines are still in the experimental stages, it is, nevertheless, possible to produce immunity to intracerebral challenge with inactivated virus in both monkeys[102] and mice.[104] The future of vaccine prophylaxis lies in increasing the knowledge of the number of virus types and their immunogenic relationships as well as by improvement in the methods of inactivating virus.

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Viruses of Poliomyelitis*

ROBERT WARD, M.D.
New York, New York

THE etiologic agent of human poliomyelitis is a virus which can be identified by the characteristic experimental disease it produces in primates, by its limited host range, by the character and distribution of microscopic lesions in the central nervous system (CNS) of the infected host, by its immunologic characteristics and by certain physical and chemical properties.

EXPERIMENTAL DISEASE

The first step in recognition of the poliomyelitis virus is to inoculate suitably prepared material into primates. Virus is most commonly detected during life in human intestinal excreta and material from the oropharynx and at postmortem from the central nervous system and contents of the lower bowel. The routes commonly used are the intracerebral, intranasal, intraperitoneal, intra- and subcutaneous and oral. The most sensitive test is usually afforded by direct contact of virus with nervous tissue. The rhesus monkey (Macaca mulatta) is the species most often employed. The chimpanzee (Pan satyrus) and the cynomolgous monkey (Macaca irus) are especially susceptible to oral administration of virus. After a variable incubation period (average of one to two weeks) the monkey may develop the typical experimental disease characterized by a fever of 105°F. or more, excitement, ruffled fur, tremors of the head and extremities followed by partial or complete paralysis of one or more extremities. Although separate involvement of most of the cranial nerves has been described, the one most commonly recognized is the seventh. The monkey may be quickly rendered prostrate and death may follow even if careful nursing care is supplied. Other phenomena exhibited by experimental animals may also resemble the disease in man. Paralysis or localized weakness may be transitory, lasting a day or so. The animal may have fever and other premonitory signs but no detectable weakness, or it may exhibit no "clinical" disturbance whatever and still present the typical microscopic lesions of poliomyelitis in the CNS from which virus can be recovered on passage.

Pathologic Changes. The typical microscopic lesions consist of necrosis of the nerve cells, neuronophagia and perivascular cellular infiltration. The character and distribution of these lesions so important in the identification of poliomyelitis virus are described in detail in Bodian's article in this series.[1]

Physical and Chemical Properties. On the basis of filtration experiments the size of poliomyelitis virus is estimated to be about 8 to 17 millimicra in diameter.[2,3] More recently Gard has reported from data obtained from the electron microscope and sedimentation and diffusion constants that the FA encephalomyelitis virus of mice is a thread-like particle 12.5 by 580 millimicra, and he has also observed similar thread-like particles in preparations made from human stools.[4] Melnick described similar rod-shaped particles in purified stools containing poliomyelitis virus.[5] The significance of these rod-shaped particles was thrown in doubt when similar particles were observed in normal children's stools which were negative for active virus. Loring et al.,[6] on the other hand, studied purified preparations of Lansing virus by electromicrography and observed slightly asymmetric particles,

* From the Department of Pediatrics, New York University College of Medicine, New York, N. Y.

with an average diameter of 25 millimicra. As similar particles have been obtained from the CNS of normal animals it is not possible to state with assurance that poliomyelitis virus has yet been seen or measured.

The action of certain physical and chemical agents on poliomyelitis virus indicates that in some respects it is a hardy virus. It has been preserved for years in the frozen state (−20°C. or −70°C.)[7] or in 50 per cent buffered glycerol at ordinary icebox temperature. Ether appears to have little if any harmful effect on the virus. This fact is especially useful in the laboratory for preparing contaminated material such as stools, sewage, etc. for inoculation into monkeys. The virus is not affected in the pH range of 4 to 10[8] nor by 1 per cent phenol. On the other hand, it is destroyed by such protein-denaturing agents as heat, ultraviolet light, chlorine, hydrogen peroxide, potassium permanganate and formalin. Recent studies have shown that it is easier to heat-inactivate certain strains of virus pathogenic for rodents when this virus is suspended in water rather than in milk.[9] By the same token the presence of organic matter appears to protect virus against chlorine.[10] It is probable that more chlorine is needed to destroy poliomyelitis virus than most bacteria[10] although this point has not been settled.[11]

Host Range. A definition of the term poliomyelitis virus is not easily made and its subgroups are not easily classified.[12] But the pathogenicity for various laboratory animals is an important step leading to its identification for, in contrast to other neurotropic viruses, most strains of poliomyelitis virus are pathogenic only for man and other primates, thus serving to distinguish poliomyelitis from various types of encephalitis virus, some of which are pathogenic for mice, others for guinea pigs and rabbits also. (Table 1.) The Lansing strain of poliomyelitis virus was first isolated and adapted by Armstrong from monkeys to cotton rats and mice.[12–14] Since then a few others related immunologically to the Lansing strain have been similarly adapted to rodents.[15,16] Reports of the adaptation of Lansing-like strains direct from man to rodents[17,18] have not been confirmed. It is striking that poliomyelitis virus has not been shown to propagate in the embryonated hen's egg; very few viruses which attack man fail in this respect. In the process of "adapting" viruses to various experimental animals one has to be on guard against the accidental recovery of agents native to the experimental host. Theiler's virus of mouse encephalomyelitis is a case in point. The TO strains of this mouse virus bear a close resemblance to poliomyelitis virus, both

TABLE 1

HOST RANGE OF POLIOMYELITIS VIRUS COMPARED WITH CERTAIN OTHER NEUROTROPIC VIRUSES

Virus	Monkey	Mouse	Cotton Rat	Hamster	Guinea Pig	Rabbit	Hen's Egg
Poliomyelitis	+	0	0	0	0	0	0
Poliomyelitis (Lansing group)	+	+	+	+	0	0	0
Theiler's (mouse encephalomyelitis)	0	+	+	+	0	0	+
MM, Columbia SK, EMC	?	+	+	+	+	0	+
Encephalitis (St. Louis type)	+	+	?	+	0	0	+
Lymphocytic choriomeningitis	+	+	+	+	+	0	+
Encephalitis (equine types)	+	+	+	+	+	+	+
Rabies	+	+	+	+	+	+	+
Herpes simplex	0	+	+	+	+	+	+

having the same size, similar reactions to certain physical and chemical agents, similar distribution in the bodies of their respective natural hosts and they are productive of similar pathologic lesions. Furthermore, only 1 of 1,000 to 10,000 mice develops spontaneous paralysis, an incidence which appears to have a remarkable parallel in human poliomyelitis. The difference in host spectrums between poliomyelitis and Theiler's virus is shown in Table 1. Immunologic methods may also serve to differentiate these agents.

The so-called MM virus and Columbia SK virus, considered by some as strains of poliomyelitis, have recently been shown to be immunologically indistinguishable from encephalomyocarditis (EMC) virus.[19,20] The host range of this group of viruses is not that of poliomyelitis and, furthermore, MM virus is killed by ether.[29] These differences indicate that by present criteria MM and Columbia SK viruses do not conform to the pattern of orthodox poliomyelitis viruses. The possibility of their relation to disease in man needs further study.

Immunologic Characteristics. The problem of multiple strains of poliomyelitis virus distinguishable by immunologic methods is fully dealt with in the article by Morgan.[21]

POLIOMYELITIS IN MAN

Distribution of the Poliomyelitis Virus. Studies of the pattern of distribution of virus postmortem in man have increased our knowledge of the natural history of the disease and, taken together with the finding of abundant virus in stools, sewage, flies and fly-contaminated food, they have served to re-orient the epidemiologist concerned with portals of entry and pathways of transmission. Instead of being found generally in all tissues and organs of the body, virus is localized chiefly in the alimentary tract and central nervous system.[22–24] In the alimentary tract virus is detectable at various levels from mouth to anus, in the washed walls as well as in the contents. Thus it was found in the tongue, pharyngeal wall with or without tonsils, the washed walls and, in separate tests, in the contents of both small and large intestines. In the CNS virus was found not generally disseminated, as in rabies and equine encephalomyelitis, but localized in certain specific areas in close agreement with the distribution of pathologic lesions and with its progress along closed neuronal pathways. Virus was detected at all levels of the spinal cord, pons and medulla, mesencephalon, diencephalon and motor cortex. None was found in the frontal and occipital cortexes, in the olfactory bulbs or anterior perforated substance. The last two, taken in conjunction with the usual absence of virus from the nasal mucosa and nasal secretions,[25,26] points away from the nose as a common portal of entry. Furthermore, the absence of virus from other peripheral collections of cells of the autonomic nervous system (salivary glands, superior cervical sympathetic ganglia, adrenal glands and urinary bladder wall) indicates no centrifugal spread to those areas. Its presence, therefore, in the wall of the alimentary tract strongly suggests that tissue as a primary site of attack and invasion.

Virus has been found but rarely in the blood[17,27] which, correlated with the previously mentioned data, indicates that the blood stream is neither an important nor necessary factor in the pathogenesis of poliomyelitis. The significance of the occasional postmortem detection of virus in certain viscera and lymph nodes is unknown.[22–24]

Elimination of the Virus. Poliomyelitis virus has been recovered frequently from washings of the oropharynx and nasopharynx, from pharyngeal swabs and from intestinal excreta. In a limited number of tests no virus was found in the urine.[25] In their summary of the literature up to 1938, Vignec, Paul and Trask[28] found that virus had been detected in material from the nasopharynx, tonsils and trachea in 15 per cent of 105 attempts made during the first five days of illness and in 7 per cent of 182 attempts made thereafter. Sabin and Ward[25] on the other hand found no virus in nasal secretions collected on cotton plugs or in

saliva from twenty patients in the first two weeks of illness. Kessel and his associates were unable to detect virus in the nasal washings of 139 patients.[23] Later Howe and his group[30,31] demonstrated virus in almost one-half of the pharyngeal swabs taken during the first three days of illness. Results were negative on swabs taken later in the disease. These findings have been generally confirmed in other laboratories.[26,32–34]

During the last decade the emphasis has been on intestinal excreta as the mode of exit in man. Numerous investigators frequently have detected virus in the stools of patients with paralytic as well as non-paralytic poliomyelitis and in those of healthy carriers as well. Virus seems to be present in higher incidence and to persist for longer periods in the stool than in material from the oropharynx. Thus Horstmann, Melnick and Wenner[35] recovered virus during the first week of illness from the stools of seven of ten patients but from the oropharynx of only two of nineteen patients tested; of specimens collected during the second week, four of seven stools, but not one of seven specimens from the oropharynx, yielded virus. Horstmann, Ward and Melnick[36] have shown that the excretion of virus in stools persists appreciably for eight weeks. The record is held by Lépine, Sédallian and Sautter[37] who detected virus in the stool of a patient as long as 123 days after onset. Of perhaps even greater interest and importance is the detection of virus in the stool *nineteen days before* onset of paralytic poliomyelitis by Brown, Francis and Pearson.[38] Similar findings have been reported in the pharynx by Gordon and his group.[34] These studies provoke a number of important questions: In what tissue is virus being elaborated that it may be excreted for so long before and after the appearance of clinical signs? To what degree is the population "infested" before an outbreak? What are the factors, controllable or not, related to the host, virus or environment which determine the conversion of inapparent or non-paralytic poliomyelitis to the paralytic form of the disease?

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Mechanism of Immunity in Poliomyelitis and Its Bearing on Differentiation of Types*

ISABEL M. MORGAN, PH.D.
Baltimore, Maryland

In this paper I will present the concept of immunity to poliomyelitis as it has been developed in the last few years. This concept has been based largely on experimental work using monkeys and chimpanzees and, for certain purposes, cotton rats and mice. Direct observations on human beings, naturally more limited in scope, will also be discussed.

Since discovery of the virus etiology of poliomyelitis, more attention has been given to the pathogenesis of the virus than to its immunogenesis, that is, the immune response which develops in the wake of infection. With the evidence available, I will give the basis for the current understanding of immunity in man, whether acquired without obvious illness or as a result of known infection. To understand the epidemiology or immunology of a disease entity it is obviously essential to know whether the causative agent is a single or multiple immunologic type. Thus an important addition to the understanding of poliomyelitis is the information we are gaining on the immunologic types of the virus.

IMMUNIZATION

Of Monkeys with Active Virus. Earlier attempts to immunize monkeys with active virus have already been reviewed.[1] Among them the outstanding ones are those of Kramer, Grossman and Hoskwith[2] and Aycock and Kagan.[3] They produced circulating antibody and intracerebral immunity in monkeys vaccinated with active virus.

In this laboratory we have also vaccinated monkeys with active virus. We have found the intramuscular route superior to other peripheral routes for inducing active immunity.[1] Monkeys vaccinated by repeated injections of active virus by this route have resisted intracerebral challenge with a large dose of the same strain of virus as used for immunization. The monkeys also developed neutralizing antibody demonstrable at a high level in the serum. Use of the Lansing strain of virus infective in rodents[4] has facilitated these studies. With this virus, it is possible to carry out quantitative neutralization tests in mice. It was found that the higher the level of circulating antibody, the greater was the proportion of animals immune to intracerebral challenge.[5] Based on these quantitative results the serum antibody level necessary to insure immunity was established. Although immune animals have a high level of antibody in the serum, that in the CNS and spinal fluid is far lower. The picture of antibody distribution in the actively immunized animal will be contrasted later with that in the paralyzed convalescent.

The effect of vaccination is not transient for antibody has been demonstrated in the serum of three immune monkeys for as long as one year after the last vaccination.

Of Monkeys with Inactivated Virus. Several investigators have attempted to vaccinate monkeys with poliomyelitis virus inactivated by a variety of agents. Some reported production of antibody but not intracerebral immunity. The more careful studies of Brodie[6,7] with virus inactivated with formalin indicated the possibility of intracerebral immunity to minimal doses of

* From The Poliomyelitis Research Center, Department of Epidemiology, Johns Hopkins University, Baltimore, Md. Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

virus. The results have been critically reviewed.[8] It may be stated simply here that although his criterion for inactivation was far better than that of earlier workers, the minimal doses used for challenge make the claim of intracerebral immunity questionable.

We have also vaccinated monkeys with virus inactivated with formalin.[8] After repeated intramuscular injections the majority became immune to a large intracerebral dose of active virus. The serum antibody level in these monkeys equalled that in monkeys vaccinated with active virus. Thus the immunogenic effect of active virus has been reproduced in monkeys by virus inactivated by formalin, more extensive immunization with the inactivated virus being required. Although this result gives promise that a safe vaccine might be developed, many obstacles will have to be overcome before considering vaccination in man. A readily available source of virus is needed. In order to develop a more efficient vaccine much animal experimentation remains to be done. Complete inactivation must be established by the most stringent tests available since with a disease of such low incidence one would not be justified in taking any risk whatsoever in the vaccination procedure. Finally, a human trial would have to be carried out for efficacy of vaccination. Because of the low incidence of the paralytic disease, this would require a vast human experiment. Gilliam and Onstott[9] have estimated, based on an expected epidemic rate, that an adequate field trial would require at least 15,000 children.

In Paralytic Convalescent Monkeys. Several investigators have studied second attacks of poliomyelitis by re-injection of monkeys convalescent from one attack. The results have been conflicting. For the present it will simplify the question to deal with results in which the same strain of virus was used for first and second inoculations. Kessel and Pait[10] reported sixty-three of sixty-five individuals refractory to second attacks after re-inoculation with the strain inducing the first attack. Bodian[11] observed no fresh paralysis in seventy-seven monkeys re-inoculated intracerebrally with the same or immunologically related strains. Howe and Bodian[12] found that monkeys uniformly failed to develop fresh paralysis when re-inoculated in an area of the CNS which had been infected earlier with the same virus. However, monkeys in which only part of the CNS had been infected were fully susceptible to virus introduced by a previously uninvaded portal. For example, they isolated the lower part of the CNS by spinal cord transection. The CNS of monkeys so prepared was then infected with virus injected into the CNS below the level of transection. When subsequently the CNS above was exposed to virus, it was found to be fully susceptible.

An interesting interpretation of these findings lies in the distribution of antibody in the paralytic convalescent animal. It was found[13] that the highest antibody levels were within the central nervous system. The areas most heavily involved with poliomyelitis, namely, the anterior horn of the spinal cord, and next the medulla, showed the greatest concentration of antibody. Non-susceptible gray matter and white matter showed little or no antibody. The level in serum, equal to that in spinal fluid, was well below that in the affected gray matter. The finding of a high concentration of antibody in the areas of the CNS most heavily involved not only accounts for the immunity to second attack but also explains why, in the experiments of Howe and Bodian, no such immunity was found in those parts of the CNS which had been isolated from the first infection.

TYPE DIFFERENTIATION OF STRAINS OF POLIOMYELITIS VIRUS BY RECIPROCAL VACCINATION-IMMUNITY

For the first two decades after discovery of the virus etiology of poliomyelitis, strains of the virus were used for experimental work in monkeys with little consideration of the relationship of one to another. The demonstration that active immunity of a high

order could be induced in monkeys in response to intramuscular injection of active poliomyelitis virus[1] has afforded a basis for type differentiation.[14] The relationship of one strain to the other can be determined by reciprocal vaccination and intracerebral challenge. This method will be illustrated by the results obtained with four strains of virus. Monkeys were vaccinated by repeated subcutaneous and intramuscular injections of active virus of one of the strains indicated in Table 1. They were then challenged with an intracerebral injection of a dose of the same virus containing 10,000 infectious units. Those which proved immune were given an intramuscular step-up dose of homologous virus and then challenged with the large intracerebral dose of an unknown virus. The large intracerebral challenge dose insures a control rate of 90 per cent or over as shown in the accumulated results at the bottom of the table.

TABLE 1

RELATIONSHIP OF FOUR STRAINS OF POLIOMYELITIS BY RECIPROCAL VACCINATION-IMMUNITY

Vaccinated with, and Immune to:	Intracerebral Challenge with:			
	Lansing	Brunhilde	Kotter	Frederick
Lansing	.....	8/8* (i.n.)	6/8 (i.n.)†	5/5
Brunhilde	4/4	.....	0/4	0/5
Kotter	6/8	0/4	.....	0/4
Frederick	4/5	0/5	0/5	
Controls	34/34	19/19	21/22	19/21

* Eight monkeys paralyzed of eight challenged.
† i.n. = intranasal challenge.

It may be seen that the response of these immune animals to the test virus is virtually all or none. The monkeys in groups vaccinated with and immune to either Brunhilde, Kotter or Frederick were also solidly immune to the other two strains. They were not immune to Lansing virus, nor were Lansing-immune animals resistant to these three viruses. The three viruses, Brunhilde, Kotter and Frederick, therefore constitute one type and Lansing another.

Fourteen strains of poliomyelitis virus have now been typed by the method of cross-immunity.[15] All but one of these have been shown to be more closely related to one than to the other of two types of which the Lansing and Brunhilde strains are prototypes. Nine fell into the Brunhilde and four into the Lansing type. The Leon virus proved to be not related to these two types and thus represents a third distinct type. Although to date three immunologic types of poliomyelitis virus have been found, the possibility remains that more types will be forthcoming as additional strains are classified.

TYPE DIFFERENTIATION OF STRAINS OF POLIOMYELITIS VIRUS BY SECOND ATTACK RATES IN CONVALESCENT MONKEYS

It has already been stated that paralytic convalescent monkeys are immune to reinoculation of the strain of virus which induced the first attack. The question of whether a different strain of poliomyelitis virus can induce a fresh attack was first clearly answered by Burnet and Macnamara[16] in 1931. Monkeys convalescent from paralysis induced by a Melbourne strain succumbed to re-injection with the MV strain from New York. The converse was also true in a single MV convalescent monkey.

On the basis of resistance of convalescents (as well as of serum neutralization tests) Paul and Trask[17] and Trask, Paul, Beebe

and German[18] also reported qualitative immunologic differences between strains. Kessel, Stimpert and Fisk[19] and later Kessel and Stimpert[20] found a difference in paralytic rates in convalescent monkeys when re-inoculated with the same compared with challenge with each of the other three viruses. It is interesting that such a second attack rate in a larger experience is quite consistently around 50 per cent. The nature of this resistance of half the animals is not fully understood. The Lansing strain was

TABLE II

RELATIONSHIP BETWEEN FOUR STRAINS OF POLIOMYELITIS VIRUS BASED ON SECOND ATTACKS IN CONVALESCENT MONKEYS

Convalescent from Attack with:	Intracerebral Challenge with:			
	Lansing	Brunhilde	Kotter	Frederick
Lansing	0/6*	1/2	1/3	3/3
Brunhilde	8/20	0/12	0/8	0/5
Kotter	4/11	0/7	0/8	0/6
Frederick	19/32	0/7	0/9	0/9
Controls	26/28	18/18	22/24	20/22

* 0 monkeys showed fresh paralysis of six challenged.

other strains of poliomyelitis virus. These reports laid the basis for the concept that all strains of poliomyelitis virus do not behave alike in monkeys convalescent from infection with one strain. Nevertheless, it was difficult from these data to obtain a clear idea of the relationships between strains.

In our current undertaking to classify strains of poliomyelitis Bodian[11] has used second-attack rate in convalescent monkeys as another means of type differentiation. Table II illustrates the relationship between four strains as established by this method. The first and second intracerebral doses each containing 10,000 infectious units were injected into both sides of the thalamus.

It may be seen that animals convalescent from one strain were uniformly resistant to second attack with the same strain. Furthermore, this resistance obtained reciprocally among the three strains, Brunhilde, Kotter and Frederick. However, Lansing challenge induced paralysis in some individuals in each group of animals convalescent from Brunhilde, Kotter and Frederick infection; and, conversely, some Lansing convalescents were paralyzed by found to be different from the other three strains which were indistinguishable from each other in these tests. Thus the relationship among these four strains obtained by vaccination-immunity is borne out by the difference in second attack rates in the convalescent.

IMMUNITY TO POLIOMYELITIS IN MAN

Naturally Acquired. Several observations bearing on immunogenesis have been made directly in man. An outstanding feature of paralytic poliomyelitis is the age incidence, the highest attack rates being in the first decade of life. Increasing evidence is accumulating that for every paralytic case there are many non-paralytic infections. Howe[21] estimates one hundred inapparent infections for every recognized case. Another pertinent observation is that with increasing age a greater proportion of the population has a circulating neutralizing antibody. Among reports of many authors that of Turner, Young and Maxwell may be cited.[22] They studied serum of 303 children and found that 86 per cent by the age of ten to fourteen years had developed neutralizing antibody to the Lansing strain. Thus it

appears that increasing antibody with the age of the population parallels a decrease in incidence in the paralytic disease. I do not mean to imply that circulating antibody, *per se*, is responsible for immunity. This is probably not the case since the blood stream is not involved in the pathogenesis of the virus. The finding of antibody in nasopharyngeal secretions[23] of individuals with a high level of circulating antibody may have a far more direct bearing on protection of the individual. This is of particular interest in view of the fact that this region, more specifically the oropharynx, is considered one of the probable portals of entry of the virus. Virus has been recovered from the oropharynx repeatedly, not only from patients with poliomyelitis[24] but from healthy children, playground contacts of these patients.[25]

Naturally acquired immunity is then explained by exposure to virus which in most individuals does not produce paralytic disease but gives rise to an effective immune response. Confirmatory evidence for this hypothesis comes from the observation that chimpanzees, also susceptible to alimentary infection, develop neutralizing antibody after receiving virus by mouth in the absence of paralysis.

Since more than one immunologic type of poliomyelitis exists, full immunity in the adult must depend on prior exposure to all prevalent types of virus.

Passively Acquired. Since naturally acquired active immunity appears to be effective in protecting against poliomyelitis, the possibility of prophylactic passive immunization has frequently been raised. So far the results by chimpanzee experiment have been negative; no evidence of passive immunity to oral inoculation of virus was obtained in three chimpanzees receiving intraperitoneal injection of large quantities of homologous immune serum from vaccinated monkeys.[26]

The use of adult human serum has been proposed for prophylaxis in children on the rationale that most adult sera have antipoliomyelitis neutralizing power (as shown with Lansing type virus). In fact, many children in epidemic areas have been given adult human serum in the hope that it might have a prophylactic effect. However, the possible beneficial effect of such treatment has never been adequately measured by a human experiment. Even if an effective amount of antibody could be given to children when an epidemic seemed imminent, the expected duration of two or three weeks of such passive immunization would be inadequate to protect children even through the remainder of the epidemic and such immunization would, of course, leave no permanent effect.

Adult human serum has also been proposed and used for therapy. However, the effect has been extremely difficult to evaluate. The best controlled study is that of Bahlke and Perkins[27] who gave human adult gamma globulin to alternate preparalytic patients with poliomyelitis (a total of 111) entering the hospital in Buffalo and Elmira, N. Y. in the epidemic of 1944. Their criteria for diagnosis of a preparalytic patient consisted of (1) a spinal cell count of 10 or more cells per cu. mm. and (2) no definite weakness of any muscle group, nor evidence of facial, pharyngeal or respiratory involvement in an individual who otherwise presented a clinical syndrome indicative of poliomyelitis. The patients were followed for six months by physicians who did not know which were the treated patients. No benefit from the gamma globulin was detectable.

As a Result of Paralytic Infection. Immunity in the human convalescent, by analogy with the convalescent monkey, is interpreted as based on the presence of high concentration of antibody in the affected susceptible parts of the CNS. Nevertheless, well authenticated second attacks of paralyzing poliomyelitis in man have been reported.[11,28] According to information now available, second attacks can be attributed to fresh infection with an immunologically different type of poliomyelitis virus.

As a Result of Paralyzing Infection. There are abundant reports of the serum antibody

status of paralytic convalescent individuals. The consensus has been that they do not differ from individuals who have had no known attack of poliomyelitis. Now that we are aware of distinct immunologic types of poliomyelitis virus it is obvious that such surveys of antibody in convalescents has little meaning unless the virus used is known to be the same immunologic type as that which produced the disease. This objection has been overcome in a recent report by Hammon and Roberts[29] who studied serum neutralizing antibody to the strain of virus isolated directly from the patient. Each of seven patients showed serum neutralizing antibody to his own strain within six days after onset of paralysis. Of the four patients in whom titrations were done serum antibody in three had risen by forty-five days but not in one at twenty-four days after onset. These results indicate that human convalescents possess circulating antibody to infecting virus by the time of onset of paralysis; the level of antibody increases by one month in convalescence.

I have tried to bring the concept of immunity to poliomyelitis, so long relegated to a separate category, up-to-date according to findings of the last few years. Now, forty years since Landsteiner[30] successfully transmitted the disease to monkeys, the picture of the disease process and the ensuing immunity is becoming clearer. We hope that further understanding may some day enable us to arrest or prevent this paralytic disease.

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Histopathologic Basis of Clinical Findings in Poliomyelitis*

DAVID BODIAN, M.D.
Baltimore, Maryland

THE purpose of this account is to consider the present status of knowledge of those aspects of the pathology of poliomyelitis which concern the clinician. If he is to establish an early diagnosis and initiate such therapy as will afford the patient a maximum opportunity for recovery, he must interpret the extremely variable clinical picture in terms of the underlying infectious process. Predominantly this involves a reaction in the tissues of the central nervous system, to which this discussion will be restricted. It is a remarkable fact that even in those non-nervous tissues from which the virus of poliomyelitis may be isolated at autopsy, its effect is so subtle that as yet it cannot be demonstrated by histologic means. Yet, so widespread is the influence of neurophysiologic mechanisms in the body and so far-reaching the effects of the virus within the nervous system, that the symptomatic picture of the disease involves the alteration of function of many body structures and is notoriously variable in character as well as in severity. With regard to the point of view to be presented in this account it should be mentioned that the data upon which it is based were obtained from detailed study of the central nervous systems (CNS) of twenty-four human autopsy cases[1,2] and from studies of experimental poliomyelitis in monkeys.[3-7]

DEVELOPMENT OF THE HISTOPATHOLOGIC REACTION

A satisfactory correlation of symptoms and of pathologic substrate depends on a clear understanding of the sequence of cellular changes throughout the disease. Naturally, the earliest changes are most informative. Several facts revealed by experimental work are important for understanding the origin of the histopathologic reaction. The first is that virus activity cannot be detected in the CNS until microscopic lesions are apparent.[6,8] The second is that the onset of virus multiplication in the CNS and of the cellular pathologic reaction precedes the onset of paralysis by at least one day, and often several days. The earliest visible changes in an infected region in the spinal cord are first, chromatolysis of Nissl substance in the cytoplasm of some of the nerve cells and, second, very mild inflammatory changes. These consist of the appearance of polymorphonuclear and mononuclear cells, initially in the perivascular region and soon thereafter diffusely in the gray matter. In later stages, such as are represented in human autopsy material, the inflammatory changes become widespread and obscure these important early details.

It is interesting that although the injury and destruction of nerve cells may be independent of inflammatory changes, the latter do not occur in the absence of nerve cells. For example, in regions of the thalamus deprived of nerve cells by means of retrograde degeneration following ablation of the cerebral cortex, the inflammatory changes of poliomyelitis do not occur even when virus is introduced directly into such areas. This suggests that although the inflammatory reaction as it develops may be complexly determined, its origin, at least, is

* From the Poliomyelitis Research Center, Department of Epidemiology, Johns Hopkins University, Baltimore, Md. Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

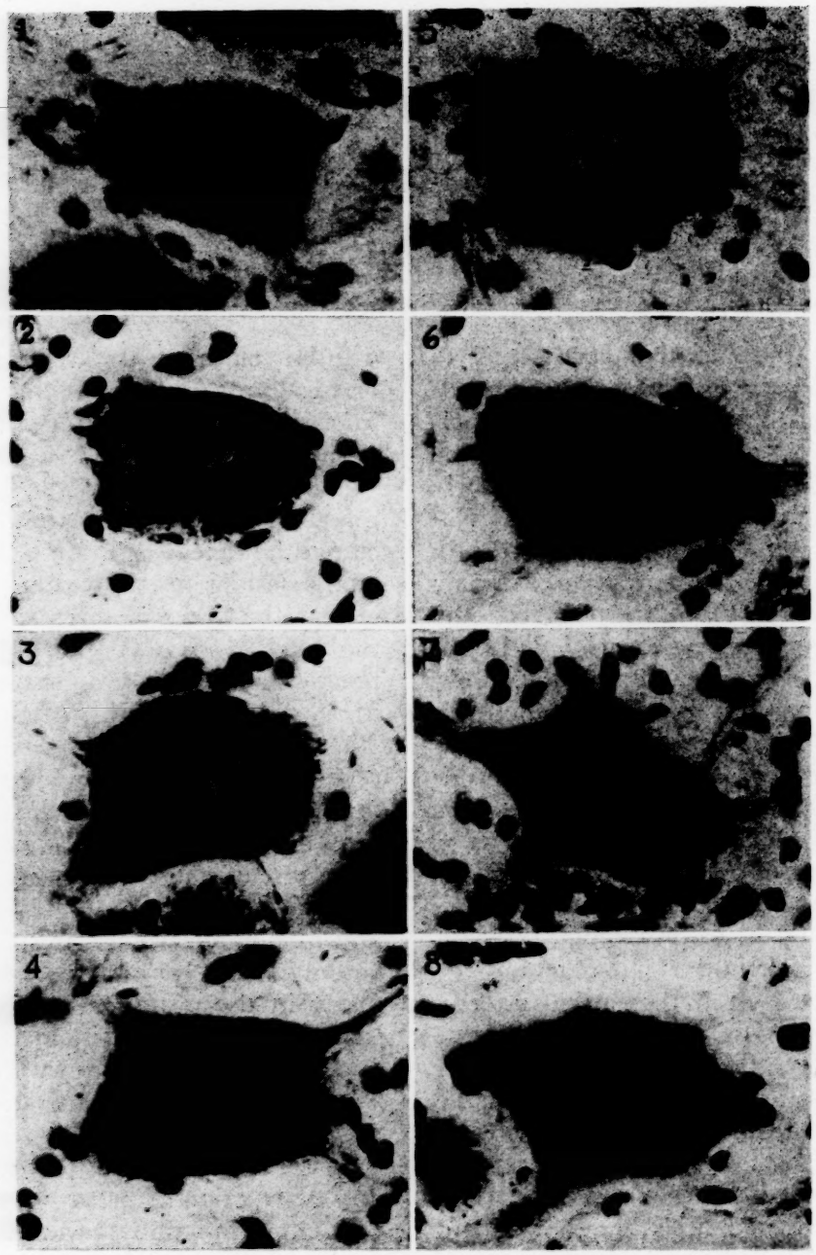

FIG. 1. Regressive stages in spinal cord motoneurons in poliomyelitis. Rhesus B_{12} first day of paralysis. (1) Normal anterior horn cell. Note massive Nissl bodies in cytoplasm, central position of nucleus, large nucleolus and dispersed chromatin; (2 to 4) early regressive stages. Note diffuse decrease in size of Nissl bodies (chromatolysis) and nucleus essentially normal; (5) severe diffuse chromatolysis, with only a few small masses of Nissl substance in cell periphery. Note clumping of chromatin in nucleus; (6) complete dissolution of Nissl bodies in cytoplasm which is slightly basophilic in staining. Nucleus is slightly shrunken and contains a small eosinophilic inclusion body; (7) cell similar to that in 6, with further shrinkage of nucleus. Note infiltrating "polyblasts" surrounding the nerve cell; (8) completely chromatolytic cell with severe diffuse basophilia of cytoplasm and of shrunken, distorted nucleus.

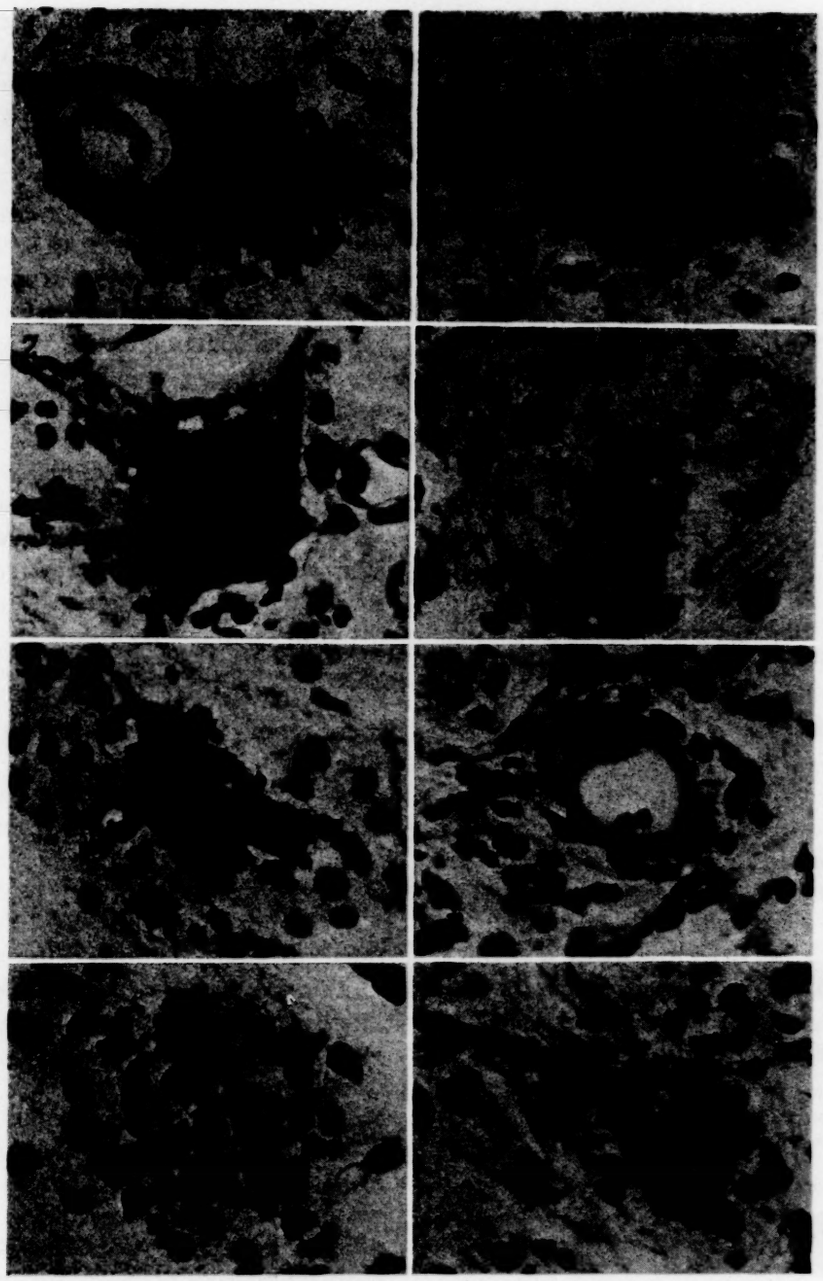

FIG. 2. Stages of degeneration of motoneurons during first day of paralysis, showing destruction by phagocytosis (1 to 4), by cytolysis (5 and 6) and by vacuolation with absorption (7 and 8); 1, 2, 3, 5, 7 and 8 from rhesus B_{12}; 4 and 6 from rhesus A696. (1) Intensely hyperchromatic cytoplasm and shriveled nucleus. Such basophilic cells are more commonly phagocytized than those which become acidophilic. Note blood capillary enclosed by cytoplasm of cell; (2) shrunken, hyperchromatic cell with granular and vacuolated cytoplasm and pyknotic nucleus. Beginning neuronophagia by surrounding leukocytes and macrophages; (3) active neuronophagia of necrotic cell; (4) macrophages and glia cells at site of a completely phagocytized cell; (5) complete chromatolysis, with no trace of basophilia in the cytoplasm. Such cells appear to be on the verge of "acidophilic necrosis" or the cytolysis and vacuolation shown in 6 to 8; (6) cytolysis of cell with shrunken nucleus showing a beaded, basophilic border. After complete cytolysis a punched-out, fluid-filled cavity is left ("falling out") which is reduced in a short time by shrinkage and the infiltration of macrophages, etc.; (7 and 8) cells in final stages of vacuolation, with surrounding and invading phagocytic cells.

dependent upon a specific reaction of the virus with nerve cells.[4]

The changes in nerve cells may occur with extraordinary rapidity so that some motor nerve cells are destroyed in the preparalytic period. The sequence of changes leading to destruction is summarized in the accompanying photomicrographs of cells found in the preparalytic and early paralytic stage in rhesus monkeys. (Figs. 1 and 2.) Many cells pass through most of these stages without evidence of surrounding inflammatory cells or exudate. It is evident that dissolution of the cytoplasmic Nissl substance is the earliest visible change and that as this progresses changes in the nucleus begin. When irreversible changes have occurred, the necrotic cell may be removed by neuronophagia due to leukocytes or macrophages, or may undergo lysis. (Fig. 2.)

The changes in nerve cells in the acute stage are accompanied by an increase of inflammatory cells which soon may reach tremendous proportions. Three principal types of such cells are found in the earliest stage, polymorphonuclear leukocytes, microglia (polyblasts, macrophages) and mononuclear leukocytes. The polymorphonuclear cells may be extraordinarily numerous in some cases but persist only for a few days. The microglia are active macrophages during the acute stage but persist in modified forms for weeks. Mononuclear cells are predominantly lymphocytic cells and are present diffusely in the tissue for two or three weeks, but persist as perivascular accumulations for several months.

GENERAL PATHOLOGIC FACTORS AFFECTING THE CLINICAL PICTURE

The signs and symptoms of poliomyelitis may vary from a few mild and transient manifestations to a great assortment of abnormalities due both to localized lesions in the CNS and to the unlocalized affects of an acute infection of the CNS. The clinical picture may therefore combine the features of an exceedingly complex and varied neurologic disease and those of a severe inflammatory process. Added to this one may have the baffling effect of a process in which recoverable injury of many nerve cells may be combined with irreversible injury to many others, in many different proportions. The principal reason for the great variability of the signs and symptoms of poliomyelitis is not the variation in the localization of lesions in the CNS but rather the variation in severity of nerve cell injury and inflammatory response in different centers. Experimental work suggests three possible factors which may determine the variation in severity of infection.[7] These are, first, variations due to differences in strains of the virus, second, reduction of severity due to previous paralytic or nonparalytic infection[9] and, third, host variation unrelated to previous immunizing experience with the virus. Although second attacks of paralytic poliomyelitis are infrequent events and apparently due to reinfection with strains of different immunologic types,[9] the known existence of at least three of such immunologic types[20] makes it probable that paralytic attacks may be rendered mild due to previous unrecognized infection with virus of a different immunologic type.

It is important to emphasize moreover that although lesions appear in certain functional centers in the CNS, symptoms attributable to such injury need not necessarily result. Such injury must reach a certain threshold of severity, varying with the margin of safety of each center before a clinical effect is observed. The evidence from experimental work and from human material is overwhelmingly clear on this point. Neuronal and inflammatory lesions may be regularly found in any susceptible center, including the anterior horn of the spinal cord, in individuals who have never exhibited symptoms which are known to follow massive injury to such centers. In experimental primates neuronal and inflammatory lesions may indeed be found in all susceptible centers in the CNS in animals who have had inapparent infections.[5] The obvious explanation of this is that severe lesions are usually necessary to

produce dysfunction at the clinical level and one must therefore look for centers which are severely involved for the site of origin of clinical signs.

EFFECTS OF THE INFLAMMATORY REACTION

Severe inflammatory reactions in poliomyelitis are usually but not always associated with extensive nerve cell destruction. (Fig. 3.) In some cases the inflammatory response in small areas may be enormous and associated at times with a small focus of tissue softening. Occasionally a small vessel in such an area may rupture, producing a petechial hemorrhage. These softenings were clearly described by Harbitz and Scheel[10] and occur only in the severest infections. Such softenings are never numerous, are rarely larger than 1 or 2 mm. in size and are not the result of vascular emboli. It is not clear whether they are the result or the cause of the very dense cellular infiltration with which they are always associated. It seems doubtful that nerve cell injury or destruction alone is responsible for such an unusual reaction since in many areas of severe nerve cell destruction the inflammatory response is relatively quite mild. It may be that local ischemia can result from the agglutination of circulating blood described by Knisely, et al.[10a] in acute cases, perhaps accentuated by the increased demand for oxygen in some severely affected areas. Since tissue rarefaction or softening occurs only in those regions which contain the specific lesions of poliomyelitis, it is apparent that local ischemia alone cannot be the cause. Perhaps the combination of severe reaction to virus and local circulatory embarrassment is responsible not only for the occasional focal rarefactions, petechial hemorrhages and softenings seen in poliomyelitis, but also those frequently described in other viral encephalitides. It is also conceivable that in small areas an unusually high concentration of virus may produce a toxic effect apart from the ordinary pathologic effect of virus multiplication in the nerve cells. Such toxic effects of influenza virus

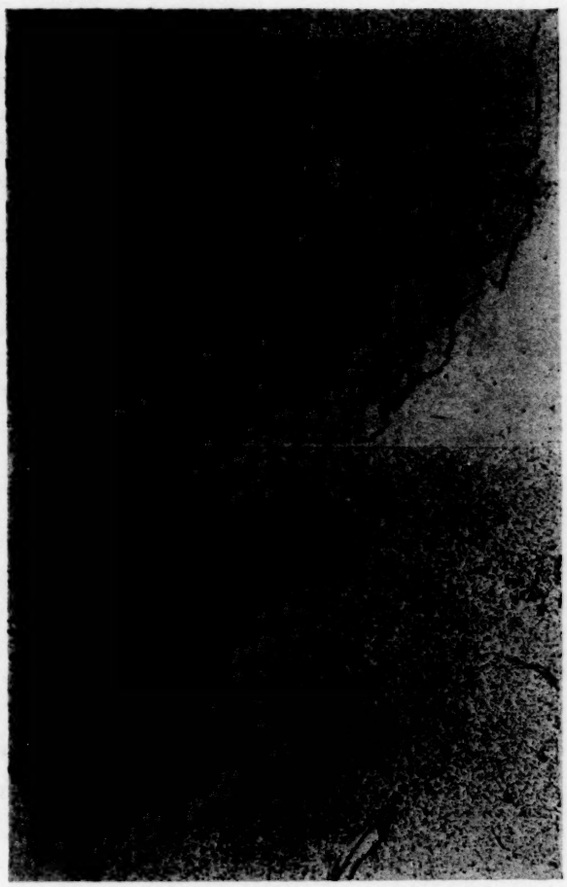

FIG. 3. Photomicrographs of human spinal cords, showing that the usual association of severe inflammatory lesions with extensive nerve cell destruction does not always occur. Gallocyanin stain, × 30. (1) Severe motoneuron loss in posterior part of anterior horn with very slight inflammatory reaction (Case H37, lumbar cord three days after onset of illness); (2) severe focal, diffuse and perivascular infiltrations of lymphocytes and histiocytes, with most anterior horn cells relatively intact in appearance (Case H34, lumbar cord twelve days after onset of illness).

have been described for example by the Henle's.[10b] These speculations simply indicate our ignorance of many of the intimate details of cellular pathologic reactions. At any rate, the focal tissue breakdown is not a primary factor in producing the paralysis of poliomyelitis since it follows the period of greatest nerve cell damage and occurs in scattered foci even in the severest cases. If it occurred more commonly in patients or more extensively in the CNS, one would hardly expect to see the high degree of recovery of function which occurs.

We have seen no evidence in our material,

experimental or human, that edema plays a dominant role in the production of paralysis, as suggested by Wickman[11] and frequently stated. Whenever a severe inflammatory response occurs in a cord segment, the cord in such an area may show swelling of the freshly cut surface. In our experience, however, an inflammatory response severe enough to produce massive exudate in the anterior gray columns usually occurs after most of the anterior horn cells in the region are already destroyed by virus action. In such cases there can be no question of possible recovery from paralysis since all or most of the motoneurons are destroyed. This occurs in monkeys with severe paralysis and in many fatal human infections. The fact that other fatal human cases show no such severity of inflammatory reaction indicates that it need not be assumed to be a regular feature of the disease and certainly not in non-fatal infections. Moreover, severe paralysis may occur without evidence of edema and, in some cases, without important vascular changes or severe leukocytic infiltration in the cord.

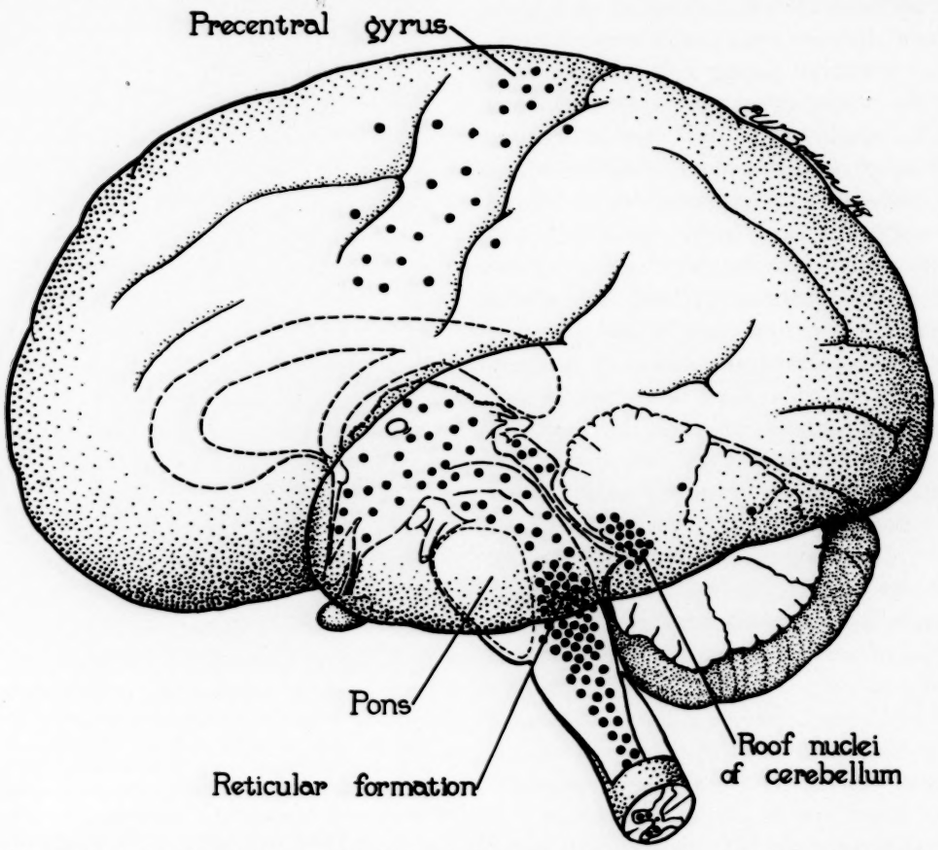

FIG. 4. Lateral view of human brain, with schematic transparent projection of the midsagittal surface of the brainstem. General distribution of lesions of poliomyelitis is indicated by large dots. Lesions in the cerebral cortex are largely restricted to the precentral gyrus and those in the cerebellum to the roof nuclei. Lesions are generally found widespread in the brainstem centers, with a number of striking exceptions such as the nuclei of the basis pontis and the inferior olivary nuclei.

DISTRIBUTION OF LESIONS

It is now well known that virus activity, nerve cell changes and inflammatory reaction are localized only in certain regions of the CNS. It has been apparent since the classical study of Harbitz and Scheel[10] that lesions of the brain are invariably found in fatal infections. In experimental animals

this includes non-paralytic as well as paralytic infections. As far as the pathologist is concerned all cases of poliomyelitis are "encephalitic." However, it is important to note that some parts of the brain rarely if ever are affected, and only certain centers are severely involved often enough to suggest that their injury produces symptoms. The regions which rarely if ever are affected include primarily the entire cerebral cortex, except for the motor area, the corpus striatum, except occasionally for the globus pallidus, the cerebellar cortex except for the vermis, and the base of the pons. In other words, the brainstem as far forward as the hypothalamus and thalamus bears the brunt of the cerebral pathologic changes in poliomyelitis and lesions in the cortex are largely confined to the motor cortex. (Fig. 4.) The characteristic distribution of poliomyelitis lesions has been shown experimentally to be due to two principal factors: first, the inherent resistance of some nervous centers to infection and, second, the restricted movement of virus along certain nerve fiber pathways.[3]

Lesions in the Cerebral Cortex. An interesting aspect of the pathology of poliomyelitis, as compared with some other virus encephalitides, is that the cerebral cortex which makes up the largest proportion of the brain substance rarely shows any pathologic changes except in the motor area of the precentral gyrus. (Fig. 5, part 1.) Even the lesions here are rarely severe and it is doubtful that they are sufficiently intense to produce clinical signs, except perhaps in rare instances. This point has been so thoroughly documented since the report of Harbitz and Scheel[10] that it is unnecessary to elaborate upon the evidence here. It has been reviewed in detail elsewhere.[1,2]

The relatively slight involvement of cerebral cortex indicates that residual behavior disturbances, as well as spastic phenomena in poliomyelitis, cannot be the result of specific lesions in the cerebral cortex. Moreover, other so-called "encephalitic" symptoms, including restlessness, drowsiness, disorientation and coma, which occurred in some of our cases were not associated with heavier than usual reaction in the cerebral cortex but rather with a greater intensity of inflammatory reaction in the brainstem, extending as far forward as the hypothalamus. (Fig. 5, Part 2.) It has recently been suggested that some of these symptoms may be due to hypoxia rather than to specific brain lesions.[12] If this is the case, there is never-

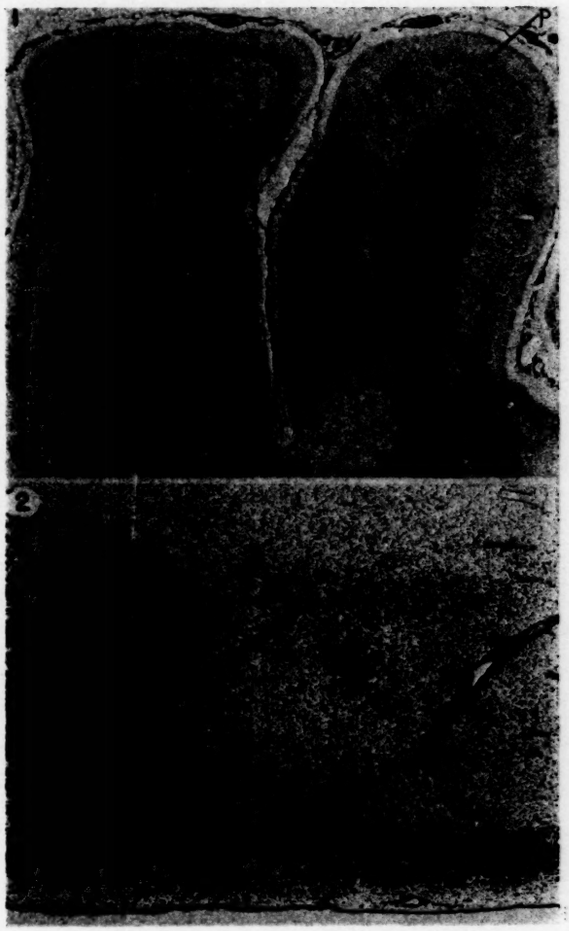

FIG. 5. Cerebral cortex and hypothalamus of a human (Case H12) nine days after onset of severe paralytic poliomyelitis. Gallocyanin stain. (1) Precentral gyrus (right) and postcentral gyrus (left) showing remarkable localization of lesions in precentral (motor) cortex only. Lesions of greater severity are rare in fatal cases and it is doubtful that they contribute significantly to the clinical picture. (× 5.) (2) Hypothalamus at level of paraventricular nucleus (below) showing severe perivascular and focal infiltrative lesions. Such lesions as well as neuronal lesions are common in fatal cases. (× 20.)

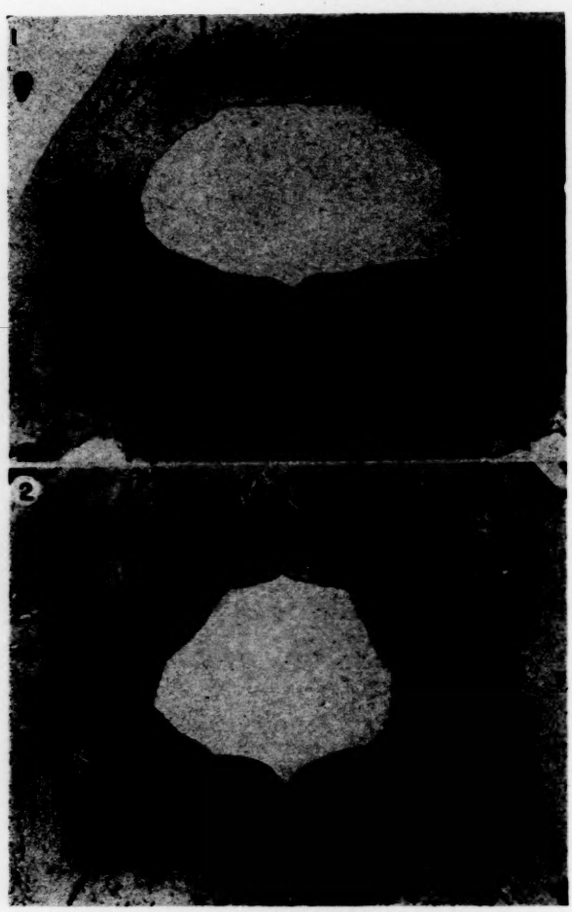

FIG. 6. The reticular formation and vestibulocerebellar centers in poliomyelitis. Gallocyanin stain. (1) Case H32 five days after onset of disease. Extensive nerve cell destruction and inflammatory reaction in reticular formation, vestibular nuclei (left) and roof nuclei of cerebellum (above fourth ventricle). Very little involvement of dentate nucleus of cerebellum (upper right). (× 10.) (2) Case H12 nine days after onset of disease. Lesions are the same as in 1 but are especially severe in the left vestibular nuclei and in the right cerebellar roof nucleus. (× 5.)

theless a correlation between "encephalitic" symptoms and severe brainstem involvement although the association may prove to be an indirect one.

Lesions in Brainstem Centers. Lesions in brainstem centers have long been recognized as being associated with fatal poliomyelitis infections[10,11] and with poliomyelitis infections in which death was not due to this disease.[1,2,3,5,13,14] The association of severe lesions in cranial nerve nuclei with paralysis of corresponding muscles is, of course, well known and obvious. What is less well recognized, however, is that most of the brainstem centers, with some outstanding exceptions such as the nuclei of the basis pontis and the inferior olives, may be severely affected in poliomyelitis. Moreover, in our series of twenty-four human autopsies there was hardly an individual who did not have lesions, sometimes of a fairly severe degree, in most of the motor nuclei of the cranial nerves as well as in the surrounding reticular formation.[1] Yet clinical signs of paralysis in the corresponding muscles were rarely recorded, except in the face, pharynx and larynx in bulbar cases. The remaining nerve cells in oculomotor, motor trigeminal and hypoglossal nuclei are generally adequate to maintain good clinical function, even in many severe bulbar infections. This illustrates the margin of safety of these centers, and perhaps also a tendency on the part of the clinical examiner to overlook mild weakness of some of the cranial nerve musclature.

The three centers in the brain most often severely affected are the reticular formation, the vestibular nuclei and the roof nuclei of the cerebellum. (Fig. 6.) The severe and extensive involvement of the former has often been recorded.[1,2,11,15,16,17] In view of the fact that a number of vital functional centers are located in the reticular formation, it is surprising, in a sense, that a fatal termination is not more common. Although material from fatal bulbar infections reveals destructive changes in the reticular formation in maximal degree, some of our material from patients who had no bulbar signs and who died of paralysis of respiratory muscles or of complications unrelated to poliomyelitis infection also showed severe lesions in this region. Rarely, brainstem damage was minimal although cord involvement was severe. (Fig. 7.) A similar case was described by Barnhart et al.[16]

In recent years certain complex functions of the brainstem have been localized in the reticular formation although not in as sharply delimited areas as those containing the cranial nerve nuclei. Experimental

evidence regarding the localization of respiratory, vasomotor, swallowing and motor inhibitory mechanisms has been reviewed by Barnhart et al.[16] Disturbances of these functions are no doubt correlated in many instances with the extensive lesions observed in the reticular formation. Guizetti, in emphasizing the presence of lesions in the reticular formation, suggests a possible role of such lesions in producing autonomic dysfunction.[15] Evidence has recently been presented that generalized spasticity in the preparalytic stage of poliomyelitis in rhesus monkeys may be due to lesions of the reticular formation[18] involving the bulbar inhibitory mechanism described by Magoun and Rhines.[19] An attempt to make a more precise correlation of respiratory and cardiovascular symptomatology in bulbar infections with poliomyelitic destruction of restricted areas of the reticular formation has been made by Brown, Baker and McQuarrie[12] (and *Am. J. Med.*, 6: 614, 1949). Large symmetrical lesions of the type they observed have not been described by others so that it remains to be seen how frequently discrete destructive lesions occur which are large enough to destroy functions apparently diffusely represented in the reticular formation. In most of our material and that described by others the lesions in the reticular formation in fatal bulbar cases were heavily peppered throughout this region rather than being predominantly composed of large discrete areas of destruction. In a few instances clearly delimited areas of complete neuron destruction were seen, as large as 1 or 3 mm. in diameter. Two of these cases have been described in detail before.[2] In one in which such lesions were in the lateral reticular formation in the region of the nucleus ambiguus on both sides death was due to respiratory failure. In another with similarly placed lesions, death during convalescence was due to acute appendicitis and no respiratory difficulty had previously been noted. There are thus serious limitations in the classification of bulbar cases according to the site of predominant destruction in the reticular formation, as attempted by Brown et al.[12] Indeed, these authors emphasize the well known overlap of signs and symptoms in bulbar infections. The reason for this overlap is apparent in the widespread distribution of lesions in the brain stem in all fatal bulbar infections.

FIG. 7. Unusual case of fatal spinal paralysis with little brainstem involvement. H40 seventeen days after onset of disease. Gallocyanin stain. (1) Section of lumbar cord showing complete motoneuron destruction and massive inflammatory reaction, especially on the left side. Note the heavy perivascular infiltrations characteristic of the subacute and early convalescent periods. (× 20.) (2) Same case as in 1 showing relatively slight involvement of the medulla oblongata. (× 10.)

At the present time it is not possible to assign clinical symptoms to the regularly severe damage of the vestibular nuclei until experimental work has shown the effect both of isolated lesions in these centers and of such lesions in conjunction with injury to the reticular formation, the roof nuclei of the cerebellum, or both. These three centers are interconnected by fiber

tracts and there is increasing evidence that they are concerned with the modification of motor activities originating in the cerebral cortex. Severe lesions in the roof nuclei of the cerebellum are fairly common in monkey and in human poliomyelitis but, although monkeys often show severe tremor in the preparalytic and acute stage, occasionally with ataxia, these symptoms apparently are relatively uncommon in human cases. When ataxia does occur in human cases, it is probably due to severe damage to the deep cerebellar nuclei. The cortex of the cerebellum is almost always free of lesions, except for scattered foci in the vermis. It is conceivable that the margin of safety of vestibular centers and of the cerebellum is great enough to preclude the occurrence of symptoms when the injury is not too massive. It is also conceivable that the nausea and vomiting seen in some cases is due to severe lesions in the vestibular region. Vertigo and nystagmus have rarely been described in spite of the frequent occurrence of severe vestibular and cerebellar lesions.

Relation of Spinal Lesions to Paralysis. In the spinal cord, as is well known, the severest lesions are always in the anterior columns. With severe cord involvement intermediate horns may also be heavily damaged and posterior horns moderately affected, but such damage is more spotty in distribution than in the anterior horns and the posterior and intermediate columns are never wiped out over whole segments as are the anterior columns at times. It is to be expected, then, that when internuncial neurons in the intermediate columns are severely affected, the neighboring anterior columns of the cord are so extremely damaged that flaccid paralysis is likely to be the only symptom referable to this region of the cord. The possibility remains, however, that internuncial neuron damage in the cord may contribute to the motor dysfunction of muscles not completely paralyzed.

An important finding in quantitative studies of experimental poliomyelitis is that most motor nerve cells in the spinal cord enlargements show morphologic evidence of virus invasion in paralytic individuals, regardless of whether the paralysis is mild or severe.[7] Since mild chromatolysis is the only sign of such invasion in many cells and can be clearly demonstrated only in well fixed material, this generalized invasion of most motor nerve cells in the spinal cord enlargements could not be confirmed in our human material. It is possible that the much larger size of the human cord is a deterrent to such widespread involvement of the spinal cord as occurs in monkeys. A few of our cases in which death occurred soon after onset appeared to have minimal lesions in the lumbar cord in the presence of severe involvement of the cervical cord. The reverse also occurred. In mild experimental cases in the first days of the disease the great majority of cells exhibit a mild degree of diffuse chromatolysis of cytoplasmic Nissl substance. In the presence of slight weakness of the muscles innervated by such cells it is clear that neurons in this state are still functional. Quantitative evidence strongly suggests that the function of infected motor nerve cells disappears only in the stage of severe chromatolysis. The widespread dissemination of virus among the motor nerve cell population occurs as early as the first day of paralysis. Motor nerve cells which are affected either are destroyed very quickly during the first few days of the disease or undergo slower recovery changes leading to complete morphologic recovery within about a month. In limbs showing complete paralysis recovery is, of course, rare and in such cases it can easily be shown that only about 10 per cent of the motoneurons, or less, have survived. Experimental material clearly shows that the degree of nerve cell destruction alone can account for most of the paralysis in the subacute and early convalescent period, and is also correlated with the degree of muscle atrophy. In the acute stage the correlation between nerve cell destruction and paralysis is not quite so high so that apparently other factors also play a role in producing paralysis. One of the most significant appears to be the

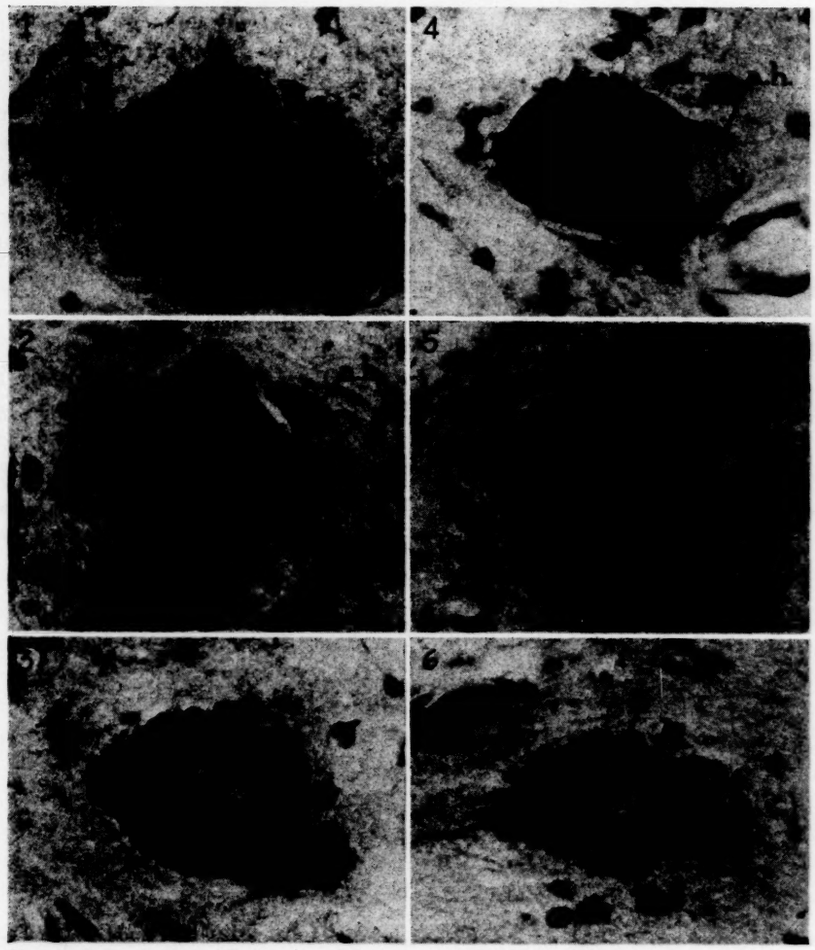

FIG. 8. Rhesus B32. Ninth day after onset of paralysis. (1) Severe central chromatolysis, with normal-appearing nucleus and accumulation of heavy masses of Nissl substance near the cell membrane. Regeneration of Nissl substance may or may not occur near the nuclear membrane; (2 to 5) similar cells but with small Nissl bodies in the central area. This appearance suggests regeneration of Nissl bodies from the periphery inward, with the area around the axon hillock (ah) last to show recovery (2, 4 and 5); (6) motoneuron of essentially normal appearance except for presence of acidophilic inclusion body (b) in nucleus. In the acute stage such inclusion bodies are seen only in cells with severe chromatolysis, suggesting almost complete recovery of such a cell.

injury of nerve cells to a degree incompatible with function but not with recovery. In all instances in which paralysis is not complete the reversible injury of many motor nerve cells by virus activity must be very common.[7] Although available human material is not adequate for this type of study, the material which we have examined and the few cases in the literature in which nerve cell changes are dealt with indicate that a similar process occurs in human poliomyelitis. In all of our human cases with a duration of disease longer than three days active neuronophagia was no longer common. In most instances evidence of active destruction of nerve cells, present in earlier cases, was absent. It is obvious that reported failures to find neuronophagia are due to the belated arrival of the observer. Within a few days after onset almost the entire degenerative phase of motor nerve cells may be terminated and the virus concentration, previously high, falls abruptly. Most remaining cells after

the early acute stage show a pattern of cytoplasmic Nissl substance quite different from the diffuse chromatolysis of this period. The remaining Nissl substance instead tends to aggregate in heavy masses near the nerve cell membrane, leaving a pale-staining central area in the center of the cell body. This appearance of central chromatolysis is characteristic of the recovery stages of nerve cells and has been shown by quantitative studies in monkeys to lead to complete morphologic recovery of most cells during the subacute stage of the disease. (Fig. 8.) The parallel changes in nerve cells and in virus concentration in the acute and subacute periods are summarized in Figure 9.

In experimental as in human cases, anterior horn cells may be destroyed either in large groups or in scattered fashion over a period of only a few days. Motor nerve fibers begin to degenerate about three days after destruction of the nerve cell body and show the typical morphologic changes as well as the time course of Wallerian degeneration. The resulting muscle atrophy follows the time course seen, for example, in Wallerian degeneration due to nerve

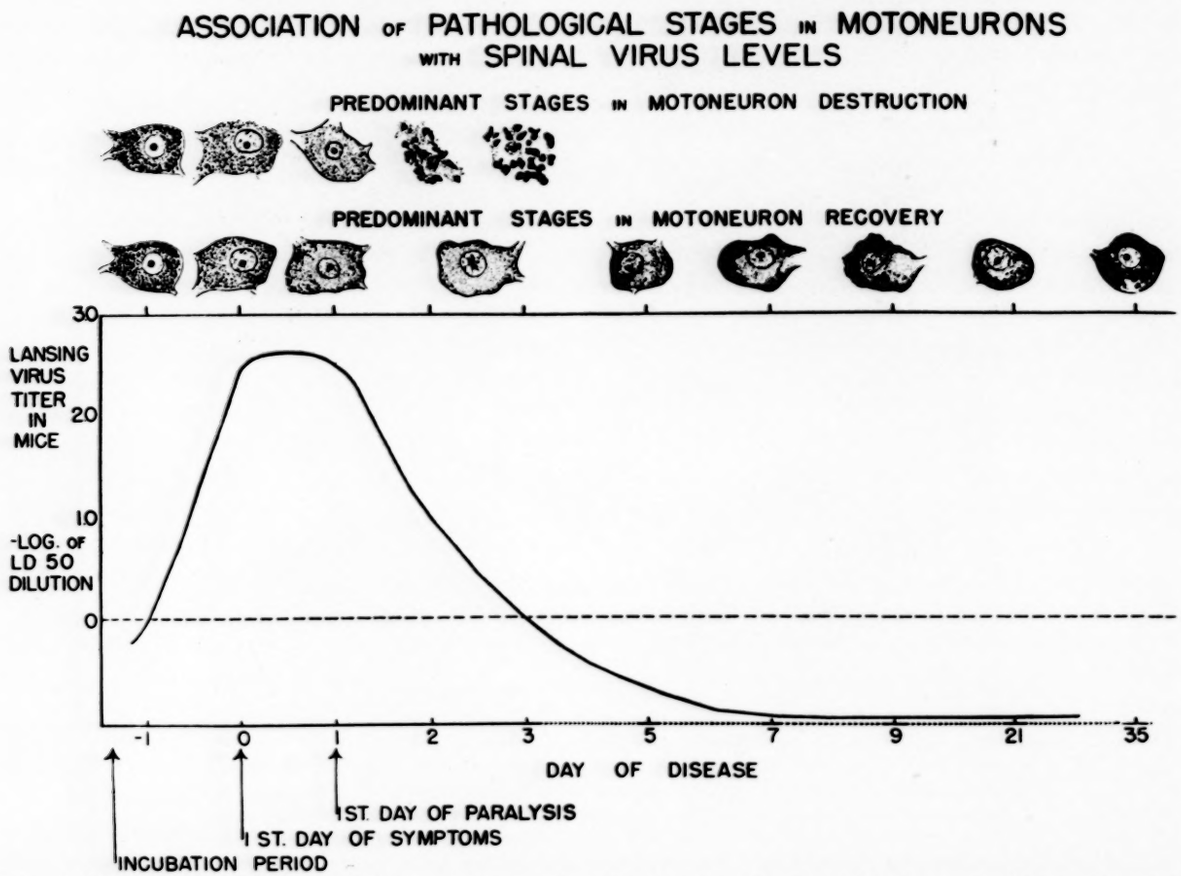

FIG. 9. Schematic representation of sequence of cytopathologic stages in motoneurons in the course of destruction and those chromatolyzed but able to recover. The approximate time course of changes is shown, with a parallel curve showing the trend of rise and decline of virus concentration in the rhesus spinal cord (from Bodian and Cumberland, 1947). Note that peak levels of virus concentration are attained at the time when the predominant stage of cell change in the motoneuron population is that of diffuse cytoplasmic chromatolysis. The curve is a partly hypothetical one, showing Lansing virus activity in the rhesus spinal cord. The curve up to the third day of paralysis is based on median values of several specimens of infected monkey cord taken at each time period and titrated in mice. The decline beyond the third day of paralysis is shown in a speculative way and is based on the decreasing probability of obtaining virus in concentrations infective by monkey passage.

section, and in cases of severe paralysis is apparent within two weeks after onset of paralysis.

OTHER SYMPTOMS AND SIGNS POSSIBLY OF BRAINSTEM OR SPINAL CORD ORIGIN

Since lesions sometimes severe are found in the posterior and intermediate horns of the spinal cord as well as in the spinal ganglia, it is possible that spinal internuncial discharge pathways and reflex pathways may be injured sufficiently to contribute to motor dysfunction. Recovery of such mechanisms probably follows a course similar to that in the brainstem centers since the two are intimately connected by ascending and descending pathways.

Symptoms in addition to paralysis which are often recorded are muscle pain, hyperesthesia and stiff neck and back. Occasionally paresthesias occur. Our material can offer no more than a confirmation of earlier findings of mild exudate in meninges and lesions of varying degrees of severity in spinal ganglia, posterior columns of the spinal cord and thalamus to account conceivably for these symptoms. In view of the rather slight involvement of these areas in many cases interpretations must be tentative. The common symptoms of neck and back stiffness are usually interpreted as being due to "meningeal irritation" but it is possible that they are the result of the same brainstem disturbances which give rise to other phenomena of spasticity in poliomyelitis. This is suggested by the frequently occurring pattern of hypertonia in postural muscles in human poliomyelitis. The frequent association of muscle pain with paralysis in the same limb suggests that this pain is the result of lesions in the posterior columns of the spinal cord or perhaps in the spinal ganglia. Lesions are found in these regions especially in segments in which severe involvement of the anterior motor columns of the spinal cord has occurred. The occasional association of pain and paralysis in the same limb does not therefore require a postulate of peripheral origin of pain in paralyzed muscles, especially since many paralyzed muscles never exhibit either pain or tenderness.

Since lesions in the cerebral cortex are largely confined to the precentral gyrus and since lesions in the sympathetic ganglia were not present in the human cases we have studied, symptoms referable to the autonomic system are very likely the result of central lesions in the brainstem or spinal cord, or both. In some cases lesions in the hypothalamus may be severe (Fig. 5, part 2) and in other cases negligible in amount. Similarly, one occasionally finds severe destruction of cells in the sympathetic motor columns of the spinal cord although this is uncommon and always restricted in extent. In contrast, lesions in the central gray of the mid-brain and hind-brain and in the mid-brain tegmentum and reticular formation are very common and often severe. It is conceivable that such lesions are responsible for vasomotor changes and other dysfunctions of the autonomic system occasionally reported in poliomyelitis. It is probable that symptoms of autonomic dysfunction would be more often observed if they were not overshadowed by the more serious symptoms of paralysis of skeletal muscles.

FACTORS IN THE RECOVERY OF MOTOR FUNCTION

Although any discussion of recovery factors must necessarily be speculative in part at this time, even a speculative analysis from the point of view of histopathology may be helpful in identifying the parts of the neuromotor apparatus which must be considered. As already stated, the cerebral cortex is so little affected by the disease process that there is every reason to suppose that the patient can rapidly begin to relearn patterns of motor activity which formerly were smoothly and subconsciously regulated by now severely damaged brainstem mechanisms.

Most of the brainstem centers concerned with motor functions are damaged in varying degree in poliomyelitis, yet an evaluation of recovery from this damage

must be phrased in very general terms until the precise contribution of each center in motor functions is better understood. It is difficult to believe that the brainstem damage does not affect motor performance even in some mild paralytic cases since such instances in experimental animals and one of our human poliomyelitis cases succumbing after fifteen days as a result of acute appendicitis (H9) showed considerable neuron destruction and infiltrative lesions in some brainstem centers, especially the vestibular nuclei and reticular formation. Recovery from such lesions should result from at least two processes, the first recovery of neurons not damaged sufficiently to be destroyed and, secondly, the re-routing of neuron-chain discharge pathways from interrupted primary paths to secondary alternative paths. The first process is probably completed in about one month, as is the case in the spinal cord, whereas the second process probably is of longer duration since it is a part of the relearning process.

In further assessing the pathologic factors which underlie the paralysis in poliomyelitis it is important to keep in mind evidence showing that reversible changes may occur in spinal motoneurons in the acute stage.[7] This means that a probably important component of muscle weakness in the acute stage may be a partial and temporary loss of function of some motor units, as contrasted with the more common occurrence of irreversible loss of function of a varying number of denervated muscle fibers due to motoneuron destruction. In fact, it seems reasonably certain from experimental data that the pathologic and recovery changes in motor nerve cells alone can account for much of the paralysis and its early recovery, respectively. The other factors mentioned probably play a secondary role although the possibility cannot be excluded that in special cases they may be more important. The slow but sometimes significant increase of power in paralyzed limbs after the third month has not been studied in detail by us because of the small numbers of cases available. Since the morphologic and probably functional status of the nervous system does not change significantly after the first and second months, such recovery as occurs after this time is probably the result of slower compensatory hypertrophy of muscle fibers with intact innervation. In our human material the entire spinal cord was available in one case surviving longer than two weeks (H40). In this case in which destruction of anterior horn cells was extensive throughout all levels, over 90 per cent of the surviving motoneurons were normal in appearance and most of the others were only moderately chromatolytic.

SUMMARY

1. Experimental evidence indicates that the onset of CNS pathologic changes occurs in the preparalytic period and is closely associated with the earliest evidence of virus activity in any particular region involved.

2. The earliest cytopathologic changes are diffuse chromatolysis of Nissl substance in the cytoplasm of nerve cells and mild cellular exudate consisting of polymorphonuclear and mononuclear leukocytes.

3. Nerve cell changes may be present in the earliest stages without inflammatory reaction in the vicinity and therefore are not necessarily the result of the latter, but rather the result of direct virus action.

4. Nerve cell changes either lead to rapid destruction of the cell or to arrest in the stage of cytoplasmic chromatolysis, following which complete morphologic recovery of the cell generally occurs over a period of about a month or less, depending upon the severity of injury.

5. Virus activity, nerve cell changes and inflammatory reaction are localized only in certain susceptible regions of the CNS, largely due to specific differences of susceptibility of nerve cells. The intensity of the inflammatory reaction, however, may be quite variable in different susceptible centers and in different individuals. Severe inflammatory reaction is usually but not

always associated with extensive nerve cell destruction. Severe nerve cell damage may occur without extensive cellular infiltration in the cord.

6. Lesions in the cerebral cortex are usually confined to the motor area of the precentral gyrus and even here the lesions are rarely severe enough to suggest that they may produce clinical symptoms.

7. "Encephalitic" symptoms such as restlessness, stupor, disorientation and coma are associated with severe inflammatory reaction in the brainstem and often with small softenings in this region. They are not associated with unusual involvement of the cerebral cortex.

8. Brainstem centers principally involved in most instances are the reticular formation of the hind-brain, the vestibular nuclei and the roof nuclei of the cerebellum. Resulting functional disturbances are discussed.

9. Widespread dissemination of virus among most motor nerve cells in spinal cord enlargements occurs in experimental poliomyelitis as early as the first day of paralysis. Motor nerve cells which are affected either are destroyed very quickly during the first few days of the disease or undergo slower recovery changes leading to complete morphologic recovery within about a month. After this time it can be shown that the degree of paralysis and atrophy are closely correlated with the number of motor nerve cells destroyed. In the acute stage, however, this correlation is not as high and other factors must also play a role in producing paralysis. An important factor is the reversible injury of motor nerve cells. Less complete evidence from human material suggests that a similar situation obtains in human poliomyelitis.

10. Experimental work suggests three possible factors which may determine the variation in severity of infection. These are, first, variations due to difference in strains of the virus, second, reduction of severity due to previous paralytic or non-paralytic infection, and third, host variation unrelated to previous immunizing experience with the virus.

The material upon which this article is based is described more fully in references 1 to 7, 14 and 18. The original illustrations of Figures 1, 2, 8 and 9 appeared in *Bull. Johns Hopkins Hosp.*, 68: 58, 1941 and those of Figures 3 to 7 in Poliomyelitis. Papers presented at the First International Poliomyelitis Conference. Philadelphia, 1949. J. B. Lippincott Co.

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Problems of the Pathologic Physiology of Poliomyelitis*

FRITZ BUCHTHAL, M.D.
Copenhagen, Denmark

IN attempting to review the pathophysiology of an infectious disease which has an especial affinity for the central motor nervous system it is reasonable to limit the discussion to an analysis of the resulting neuromuscular disorders.

Such an analysis must, unfortunately, be limited since it demands a thorough knowledge of the normal physiology of motor function, a knowledge which is in many respects far from complete. In addition, utilization of material derived from clinical and pathologic research is often difficult due to the impossibility of controlling the conditions to a degree in any way comparable with a physiologic experiment, and only rarely can the complicated pathologic changes in the physiology be studied by direct experiment. Consequently, discussion becomes of necessity speculative and theories have to be modified repeatedly as further evidence accumulates.

In poliomyelitis, as in a number of other diseases, it has been of the utmost importance for the systematic study of its pathogenesis that analogous conditions be reproduced experimentally in animals and that manifestations of the disease be studied under controlled experimental conditions.[40] The histologic changes in poliomyelitis are closely similar in primates and man, both with regard to type and distribution of the lesions although we must remember that the development and manifestations of the disease in its initial stages may vary with different portals of entry of the virus.

Discussion of the pathophysiologic features of poliomyelitis must be based primarily on the histologic lesions which occur in the different stages of the disease although the lesions, both in human and experimental poliomyelitis, show a confusing lack of parallelism with the clinical manifestations in regard to both localization and severity. Clinically, poliomyelitis is primarily a lower motor neuron disease with segmental distribution, yet all observers agree that the histologic lesions are never confined to the spinal cord but are found in a number of other parts of the central nervous system, including the precentral areas of the cerebral cortex. The central motor disturbances are few compared with the rather severe damage found in the motor cortex and in the subcortical centers coordinating motor activity; this is another clear indication of the well known potentiality of different parts of the central nervous system for substitutional activity. Similarly, although severe damage is frequently found in different parts of the medulla oblongata, the occurrence of central respiratory paralysis is, fortunately, rare. On the other hand, the disturbances in emotional behavior which may occur even in non-paralytic cases might be explained by involvement of the hypothalamic centers.[61]

In contrast with the older concept of the disease as primarily an interstitial injury the study of experimental poliomyelitis in monkeys has shown beyond doubt that it is the nerve cells which are primarily affected. The virus spreads by way of the axon[23] and it is the large anterior horn cells, especially those in the cervical and lumbar enlargements, which are partic-

* From the Institute of Neurophysiology, University of Copenhagen, Copenhagen, Denmark. Part of this paper was presented at the First International Poliomyelitis Conference, New York, 1948.

ularly susceptible. The inflammatory reaction is secondary. Bodian and Howe[7] have produced convincing evidence that the presence of living nerve cells is necessary for production of the inflammatory phenomena. When the nerve cells of a center are allowed to degenerate before inoculation with the virus, no inflammatory reaction is produced there although the opposite side, without previous degeneration, shows both nerve cell degeneration and a typical inflammatory response.

Any sign or symptom from the central nervous system might be explained by a diffuse inflammatory reaction, but it seems worth while to attempt a correlation between direct nerve cell injury and the pathophysiologic signs before taking into consideration an accessory influence of edema or other secondary factors.[57] Since in many cases a good deal of muscular function is regained in previously paretic muscles in the course of the first months of the disease,[37] such a correlation will require the assumption of a possible reversibility of the changes in certain virus-infected parts of the central nervous system. The recovery could, of course, be easily explained by the disappearance of the interstitial mesodermal reaction with its mechanical effects, and it will be difficult to exclude this reaction as a causative agent, but it must be borne in mind that the initial manifestations of the disease usually correspond with specific localizations in the anterior horns. Thus, although nerve cell necrosis and inflammatory infiltration have occasionally been found in the dorsal root ganglia, impairment of sensibility is exceptionable. The absence of sensory changes may, of course, be due to the difficulty in detecting small changes in sensibility by ordinary clinical means and, in fact, studies of the vibratory sensation have in some cases[28] but not regularly* revealed a lowered threshold indicating a hyperesthetic type of response. The degree of inflammatory reaction as reflected in the spinal fluid has no direct correlation with the progression and reversibility of pareses; furthermore, in poliomyelitis, even in the preparalytic stage, synchronized activity of different motor units of the same muscle has been observed while in cases of meningomyelitis with evidence of a diffuse inflammatory response this abnormal type of innervation has never been observed except when definite pareses also indicated the presence of anterior horn cell lesions.[18] In my own opinion these observations favor the assumption of a reversible lesion in certain nerve cells. Alternatively, recovery might be interpreted in terms of a substitution of damaged primary internuncial pathways by secondary "delay paths" in the internuncial pool. A comparison of the electrical activity of the spinal cord under the influence of edema and anoxia with that in experimental poliomyelitis might make further differentiation possible. A detailed cytologic analysis by means of more quantitative histochemical methods might also yield useful information with respect to the concepts of reversibility and substitution. An investigation along these lines might even throw light on the important finding that both cooling in water for thirty minutes and exhausting muscular effort during the incubation period of experimental poliomyelitis result in a statistically significant higher incidence of paresis and a more severe degree of motor impairment than is found in controls.[41]

The distribution of muscular involvement has given rise to various speculations. In most epidemics the muscles of the lower limb are affected with twice the frequency of those of the upper limb. In the former the quadriceps, anterior tibial and peroneal muscles are mainly affected while in the latter the deltoid, triceps and biceps are affected more frequently than the muscles of the forearm and hand. Recently Hodes[34] made an interesting attempt to explain this distribution. It is well established that there

* Dr. M. Iversen has recently examined vibratory sensation in four paralytic cases of poliomyelitis, two during the acute and two during a later stage, without finding significant deviations from normal values for threshold and adaptation.

is a close relation between velocity of conduction along a nerve fiber and its diameter. He has measured the conduction velocities in nerves to different muscles in both normal and poliomyelitic subjects and has found that the maximal rates of conduction in nerves to paretic muscles are reduced, a finding which is attributed to selective destruction of the motor neurons with fibers of large diameter, the neurons with fibers of small diameter having relatively less affinity for virus. This agrees with the fact that the proximal muscles are more commonly affected than the distal muscles. The largest motor fibers which innervate some of the muscles of the forearm are of greater diameter than the largest fibers innervating the small muscles of the hand. In addition, in earlier experiments it had been shown[55] that large, heavily myelinated fibers more commonly degenerate than the thinly myelinated or unmyelinated. Further studies of this type might also provide an explanation of the difference in susceptibility of neurons innervating the different proximal muscles of the lower limb.

Recovery after paresis depends both on its severity and on which muscle is affected; the patient's age has not been found to have a significant influence on the degree of recovery.[61] Clinical estimation of the recovery often meets with difficulties due to the scarcely detectable but increasing participation of synergists. Electromyographic examination has shown that recovery in an individual muscle may continue for at least six months. Synchronous activity of different motor units in a muscle, outlasting the third week of the disease, was found to have a less favorable prognosis for the muscle than continuous asynchronous activity in equally paretic muscles. With regard to the recovery of activity in different muscles, the prognosis is considered to be best in the flexor muscles of the fingers, knee and elbow while antigravity muscles and the small muscles of the thumb and foot are claimed to have a lower recovery rate.[61] In searching for an explanation of this difference in the behavior of different muscle groups, differences in the vascularization of different parts of the anterior horns would appear to offer a likely solution. According to Bok,[9] the cord representation of extensor and abductor muscles in various animals including primates is mainly found along the edges of the anterior horns while the cells supplying flexor and adductor muscles are situated centrally. Temporary anoxia of the lower part of the spinal cord results in cell destruction in the central region of the anterior horns, accompanied by flaccid paresis in the flexor and adductor muscles while the antigravity muscles display a considerable degree of spasticity.[38] Since (at least in rabbits) the arteries split up into capillaries mainly at the peripheral parts of the anterior horn, the periphery, representing the extensor muscles, can appropriate more of the available oxygen than the central cells. These observations make it difficult to account for the better recovery of flexor muscles on the basis of circulatory differences at the site of their cord representation.*

Paresis of the urinary bladder, with retention and overflow, and of parts of the gastrointestinal tract belong to the reversible affections in poliomyelitis. Opinions differ widely about the pathophysiology. Fanconi[24] considers it an infrequent secondary complication (in 2 per cent of 375 paralytic patients) and interprets it to be due to weakness of the abdominal muscles. Other observers have found urinary bladder paresis in 20 to 65 per cent of paralytic patients; it may occur before the somatic muscles in the extremities are affected. While in the bulbar form of the disease cerebral factors are probably involved in the pathogenesis of urinary bladder paresis, it seems otherwise most likely that the paresis of the urinary bladder, and of the descending colon (causing constipation),

* A discussion of peripheral regenerative phenomena, such as compensatory hypertrophy and outgrowth of axon branches which are important factors in recovery, would be beyond the scope of this paper.

are due to involvement of their parasympathetic innervation. The bladder and descending colon belong to the few viscera having an intramedullary representation of their parasympathetic control derived from small multipolar nerve cells scattered around the base of the ventral horn in the sacral region of the spinal cord. Normally the bladder and the descending colon contract in response to impulses from these cells. The high rate of recovery of these functions may be due either to a temporary lesion of these cells or to an independent automatic activity regulated from peripheral ganglia. The last would be an indication of the large margin of safety which assures the function of autonomic organs.

Stiffness of the muscles of the neck and spine are considered to be signs of a meningeal reaction; they appear early, in the preparalytic stage of the disease. The inflammatory response of the meninges is not very pronounced and its manifestations in the spinal fluid are less marked than in bacterial meningitis. This makes it difficult to interpret the meningeal signs in terms of an inflammatory root involvement. There are other differences between the "meningeal" reaction in poliomyelitis and in true meningitis. McDonald[52,67] found stiffness of the spine in 80 per cent and stiffness of the neck in 65 per cent of 128 patients with poliomyelitis. In true meningitis stiffness of the neck is usually accompanied by a slight contraction of the hamstring muscles (Kernig's sign), indicating a generalized increase in flexion reflex activity. Although anatomically this is an extensor movement, Fulton[29] therefore considers it a part of a flexion reflex to nociceptive stimulation.

In the meningeal phase of poliomyelitis, in contrast with true meningitis, stiffness of the neck is by no means regularly associated with other signs of flexor reflex activity. It was found to be absent in 70 per cent of McDonald's 128 patients. Further, rigidity of the neck and spine muscles is unlike that seen in meningitis; it can be overcome by slight resistance[62] and it is striking that the spastic contractions diminish or disappear with the patient in a prone position, a phenomenon which can be produced neither in meningitis nor in the meningism caused by other noxious stimuli such as subarachnoid hemorrhage.[19] Probably this relaxation follows from the inhibition of an exaggerated extensor reflex by slight extension of the flexor muscles of the neck and can be explained in terms of reciprocal innervation.[47] The stiffness of the muscles of the neck and spine could thus be due to the impairment of central inhibitory mechanisms by early lesions in subcortical centers. The release of both flexor and extensor reflexes is accompanied by repetitive discharges which reach the anterior horn cells. In the case of certain extensor reflexes the "after-discharge" may last for several seconds and is due to continuous discharges in internuncial circuits spread over several segments of the cord.[26, 43, 44] Inhibitory impulses from vestibular centers and the reticular formation of the medulla oblongata[50, 51] normally regulate the internuncial activity. Early lesions in these centers could be responsible for exaggerated after-discharges in postural contractions from the muscles of the neck and spine.

In experimental poliomyelitis spasticity can be present at an early stage at which neither virus nor histologic lesions are detectable in corresponding parts of the spinal cord while pathologic changes in the brain, especially in the reticular formation, are fully developed.[6]

The occurrence of "spasm" in paralytic and non-paralytic muscles has been the subject of intensive discussions and controversies. It is well known that in early poliomyelitis both hyperactivity of the stretch reflexes and clonus occur but are soon followed by their diminution or disappearance. The occurrence of muscle spasms in both paretic and unaffected muscles of the limbs during and after the acute phase of the disease is thought to contribute considerably to disability.[59, 60] The conception of spasm in poliomyelitis has not always

been clearly defined, but most investigators consider it to be the result of increased myotatic reflex activity. This increase which, as already mentioned, does not exhibit itself by high, deep reflexes, is thus of an entirely different type from that which characterizes, for example, the response of the muscles of a spastic spinal paresis to slight passive movements. Recordings of action potentials have shown that passive stretch is associated with discharges of longer duration than in the normal.[11] However, this effect—interesting enough when present—is very variable from epidemic to epidemic and sometimes many large groups in an epidemic are free from spasm even when tested with action currents. This agrees with our observations in forty-seven patients in 1942[18] and more recently in twenty-seven patients during the 1947 epidemic.[19] In these cases there was neither activity at rest nor did passive movements show reactions in any way deviating from those of normal muscle. Thus there is a definite difference from the true spastic activity which almost regularly occurs in the muscles of the neck and the spine. However, the sustained activity observed by several investigators is a very interesting phenomenon, provided it occurs with passive movements too small to pass the threshold of pain which may be rather low in these muscles.

The pathophysiologic explanation of this spastic activity is still open to discussion. It has been explained[11] by assuming a replacement of the single neuron reflex arc, normally responsible for myotatic activity, by multineuron arcs, possibly associated with the disappearance of inhibitory impulses. In this connection it is interesting to recall that the histologic changes are never confined to the anterior horn cells alone but are seen also in the internuncial cell groups at the same levels. Kabat and Knapp's[35] suggestion, that lesions of the internuncial cells in regions of the cord where the anterior horn cells proper are hardly affected might explain spastic reactions, has been refuted by other investigators.[6,22]

Muscle pain is felt especially when the muscle is contracted. It occurs early in the disease, mainly in the muscles of the lower limb and often in those muscle groups which later become paretic. Apparently it is of purely peripheral origin and there is no evidence of root involvement. Although it may be compared with sensations after vigorous exercise, it is hardly caused by latent "spastic" activity. It is not relieved by curarine.[27,54] The origin of pain and tenderness in poliomyelitis is still obscure as it is in a number of other infectious diseases (e.g., influenza) and in the majority of cases of local palpable muscle affections. Only in less than 20 per cent* of forty-six patients suffering from these affections did resting muscles show a constant activity which did not disappear with adequate relaxation, diverting the attention or a change of position.[14] However, in the majority of painful affections the electromyogram does not differ from that of normal muscle. It is possible that the changes in the capillary blood circulation, which Knisely[36] has observed in experimental poliomyelitis and in a number of other pathologic conditions, give rise to foci of anoxia in muscle and that the abnormal metabolites produced in these foci stimulate the pain endings which are especially numerous near the blood vessels and the tendinous insertions of a muscle; the latter position is in agreement with the localization of muscle pain to the insertions. Other factors causing stimulation of the pain endings cannot, however, be excluded and a more extensive use of muscle biopsy may yield information on this problem.

Ordinary methods of electromyographic examination have also proved useful in the assessment of paresis and of the stage of denervation in poliomyelitis when applied to studies of voluntary and electrically induced activity.[2,15,32,58] They make it possible to determine whether the paralysis is complete or not and provide a delicate means of assessing the condition of the

* This figure refers to chronic, therapy-resistant patients with intermuscular fibrositis.

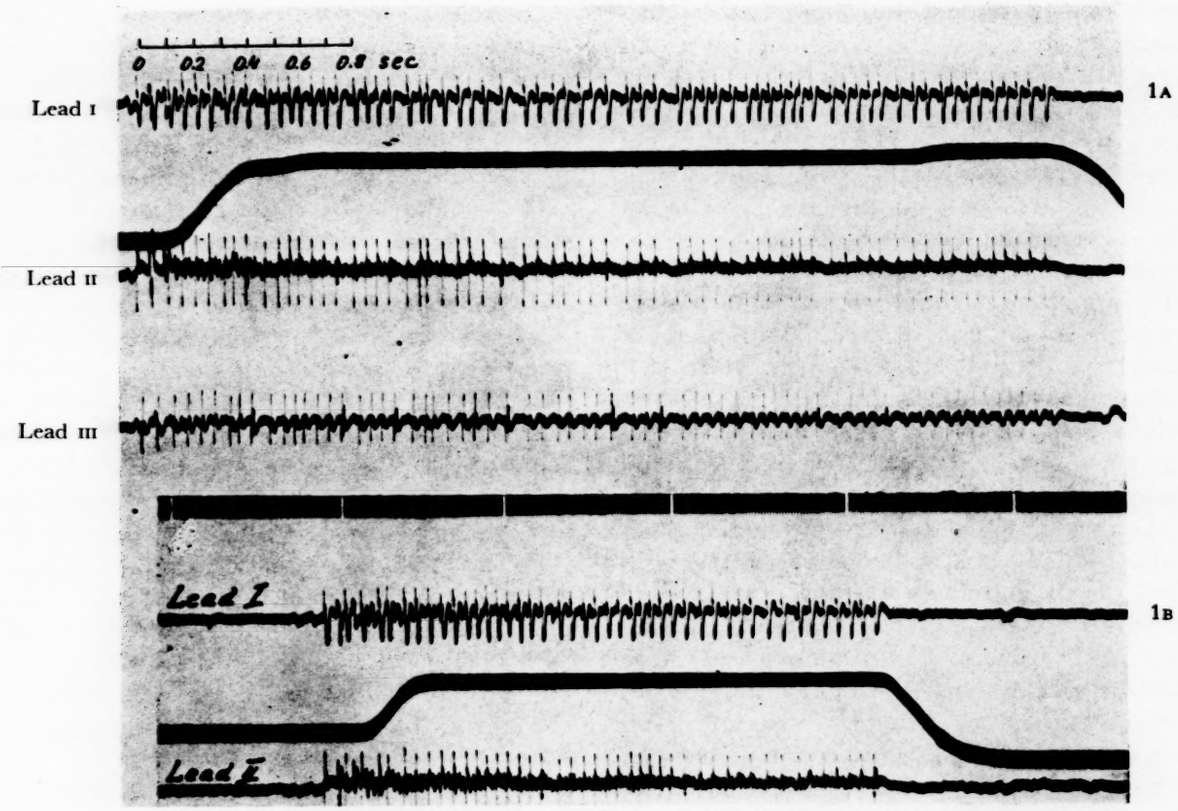


FIG. 1. Action potentials and mechanical response of paretic biceps muscle (previous poliomyelitis).[14] A, lead I: concentric needle electrode, frequency 17.3/second. Lead II: two needle electrodes 15 mm. apart at a distance of 2 cm. from lead I, frequency 17.3/second. Lead III: concentric needle electrode at a distance of 2 cm. from lead II, frequency 17.3/second. B, as A, frequency in all three leads 18.6/sec. Distance between time marks 10 milliseconds.

motor nerve and corresponding nerve cells. They can give an expression of the number of active nerve cells and detect minor degrees of lower motor neuron damage.

When the number of active motor units is reduced, as is the case in poliomyelitis and in partial lesions of the peripheral nerves, individual spike potentials can be recorded during maximal effort without interference from the activity of neighboring fibers. In genuine muscular atrophy maximum contraction is generally accompanied by the interfering electrical activity of many motor units since even slight contractions demand a wider spread of innervation than in normal muscle; it is therefore more difficult to record single discharges in these cases than in normal muscles or in muscles with neurogenic paresis.

In slight paresis the electromyogram may show a transitory state in which, although such interfering activity is found, the activity of the neighboring units is so reduced that the fiber situated nearest to the electrode dominates the curve.[15] Isolated action potentials, together with the presence of "silent areas," are found in severe paresis and correspond to the histologic picture of the loss of numerous motor units where only scattered islands of normal tissue are seen on a background of degenerated muscle tissue. In mild atrophy large and small patches of degenerated tissue occur in the midst of normal tissue and correspond to a lesser decrease in the number of active motor nerve cells and of muscle fibers controlled by them. The histologic picture of sharply demarcated patches of atrophy is typical

of these lesions in contrast to the more diffuse distribution of changes in purely myogenic atrophy. By electromyography it is also possible to distinguish between degenerative lesions of the lower motor neuron and affections in which there is temporary impairment of conduction in the axon. In denervation, fibrillation gives rise to a characteristic action potential of extremely short duration (one to two milliseconds).[65] It is presumably this type of potential which has been recorded several weeks after the initial stage in poliomyelitis as in other forms of denervation.[58,63] The reappearance of motor unit potentials of normal duration (five to ten milliseconds) can be considered an early sign of recovery. The origin of the fibrillation is still obscure; it is scarcely affected by curarine and cannot be explained by assuming increased formation or delayed destruction of acetylcholine.[53]

By leading off simultaneously from different regions of the same muscle, i.e., from different motor units the atrophy can be further differentiated since synchronous activity has been observed when the anterior horn cells are affected. This synchronization occurs during both weak and strong contractions. (Fig. 1.)[15,16] In nonfatigued normal muscle and in muscle with neurogenic atrophy caused by diseases of the nerve roots or of the peripheral nerves, synchronous activity may occur as a transient phenomenon but it did not continue after the appearance of variation in frequency with variations in contraction intensity. In amyotrophic lateral sclerosis and spinal muscular atrophy it has been found in muscles before they showed any other signs of involvement. In poliomyelitis, as already mentioned, it can appear as early as one day before the onset of paresis. (Fig. 2.) This points to a connection with partial damage to some nerve cells. Neither a compensatory mechanism to mobilize simultaneously the largest possible number of remaining motor units in a given muscle, nor a manifestation of disturbances in reciprocal innervation characterized by

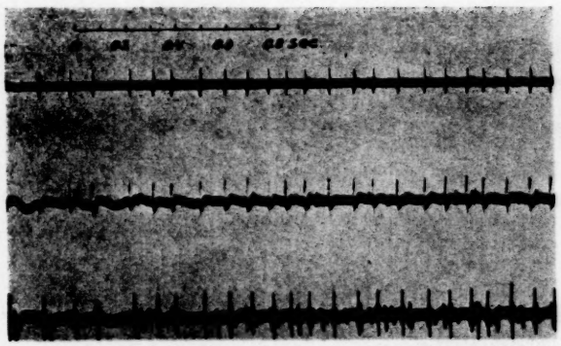


FIG. 2. Synchronous activity in a paretic vastus medialis in the initial phase of poliomyelitis.[17] Three concentric needle electrodes inserted to different depths 2 cm. apart. Distance between time marks 10 milliseconds.

simultaneous activity in agonists and antagonists of the same movement seems a likely explanation. On the other hand, synchronous single impulses also may rarely occur in two different muscles, although only in the most severely paretic stage and in contrast with the disturbances of reciprocal innervation to be mentioned this effect is irreversible.[64] It appears to the author that the same interpretation would apply here as he suggested to follow for the occurrence of synchronization in the same muscle. When testing for synchronization of potentials in the same muscle, technical artefacts have to be eliminated,* but a discussion of these problems would go beyond the scope of this paper. In extreme degrees of neurogenic atrophy, of whatever origin, there is an increased chance of picking up potentials from the same motor unit with different electrodes; this possibility must always be excluded when "true" synchronization of different motor units is used for differential diagnosis. However, when cautiously evaluated, its occurrence is a useful aid to diagnosis. For instance, in seven patients with polyradiculitis, some of them examined in the acute stage, no synchronous activity could be found despite severe

* This can be achieved by procedures which are familiar from similar electrophysiologic problems, i.e., mainly by using differential amplification and by leading off with symmetrical electrodes using a platinum cannula with two thin isolated platinum wires at a very short distance. Obviously a more primitive technic[49] demands special precautions and experience in avoiding artefacts.

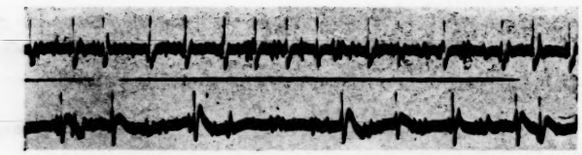


FIG. 3. Increasing fatigue in tibialis anterior with neurogenic atrophy of peripheral origin. The lower record is a direct continuation of the upper. Concentric needle electrode.

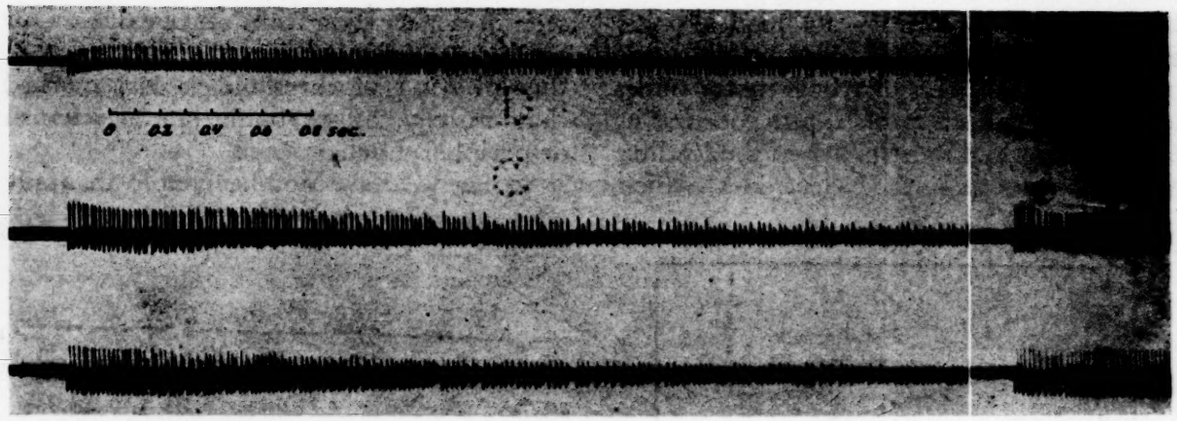
paralysis and reduction in the number of motor units.

The cause of synchronization must still be discussed on a somewhat hypothetical basis. It has been observed in decerebrate cats during myotatic activity.[5] However, in cases of anterior horn cell damage there did not seem to be any positive correlation between the occurrence of synchronization and the presence of exaggerated stretch reflex activity; on the contrary, in most cases there was evidence of diminished myotatic response. In the physiology of the nervous system synchronization of excitation processes has been considered to be due to the interaction of neighboring cells discharging rhythmically.[1,12,25,56] Partial injury of a nerve cell could facilitate an irradiation of impulses without otherwise disturbing its function and this assumption agrees with the observation that in a muscle with synchronized activity, as in poliomyelitis, the start of volitional contraction is frequently accompanied by muscle action potentials of relatively high frequency. Both normal and neurogenically atrophic muscle without synchronous innervation can begin a contraction with relatively low frequency. The high initial frequency in a muscle showing synchronization could be caused by mutual spreading of excitation (spatial summation) reaching the nerve cells with a minor and decreasing phase difference. Another explanation would be a retained activity of nerve cells with high synaptic concentrations and common internuncial pathways, and this would be compatible with the observation that mainly the spike potentials of higher amplitude are found to synchronize.

Attempts recently have been made in this laboratory to obtain a quantitative expression of synchronization of different motor units using electronic counting devices which directly give the percentage coincidence of impulses from different regions of the same muscle.[20] These investigations, although still at a preliminary stage, have given promising results. In normal muscle at a given frequency range the degree of coincidence is only slightly greater than that which can be expected statistically (3 to 4 per cent). During fatigue coincidence increases considerably (20 to 35 per cent) but it never reaches the level which is found in nearly all cases of affections of the anterior horn cells (80 to 90 per cent).

Simultaneous discharges to both agonist and antagonist is a most important disturbance of normal reciprocal innervation which has been observed in poliomyelitis.[10,11,63,64] It belongs to an abnormality which can be overcome by re-education and may be compared with the initial behavior of a flexor muscle (e.g., biceps femoris) after transposition to the extensor side.[66] In the first stage the transplant still receives impulses in the flexor phase of a movement. However, after only a few trials, in which visualization of the task seems to be more important than actual visual control and proprioceptive hints, it can also contract in an extensor phase. For some time it contracts in both phases and there is no evidence of automatic recovery of normal reciprocal innervation; then, after a certain period of practice the transplanted flexor is inactive during contractions of the other flexors. However, even years after transplantation, relapses to its native function may occur and are considered to be evidence that re-education does not replace the elementary motor mechanisms for flexor activity but rather that the substituted action develops at higher coordinating levels and can effectively outdo but not abolish natural coordination.

A similar mechanism could explain the re-coordination of certain movements in poliomyelitis when part of a synergy remains permanently paralyzed. At present,



4A 4B

FIG. 4. Paresis after previous poliomyelitis,[17] three concentric needle electrodes in vastus medialis. A, fatigue with gradual decrease in the amplitude of action potentials; B, after about 1 minute rest.

however, it is difficult to decide at what level of the cord to look for the primary disturbances of reciprocal innervation. Evidence has recently been brought forward that internuncial activity is not necessarily involved in the inhibition of the antagonist which characterizes reciprocal innervation.[45,46] Interference from the internuncial pool with monosynaptic motor activity might possibly account for disturbances in reciprocal innervation. In animal experiments a definite correlation has been demonstrated between the different phases of the slow cord potentials and the periodically alternating discharges in flexor and extensor muscles. The direction of these potentials is at the same time associated with facilitation (root positivity) or inhibition (root negativity) of flexor reflex activity.[4] Phenomena of periodic facilitation and inhibition might result from these slow cord potentials and knowledge about their behavior in the poliomyelitic animal might contribute toward elucidation of the mechanism responsible for the disturbances in reciprocal innervation.

So far the evidence of a peripheral element in the impairment of motor function has not been discussed. However, unquestionable signs of peripheral motor alterations, apart from atrophy, do exist. Fatigue in both normal and paretic muscle, independent of the cause of the paresis, manifests itself as a reduction in the number of action potentials and not as a significant decrease in the amplitude of the individual spike. (Fig. 3.) This applies to poliomyelitis in the first four to six weeks, but in its later stages an entirely different effect of fatigue is seen, i.e., the amplitude of the

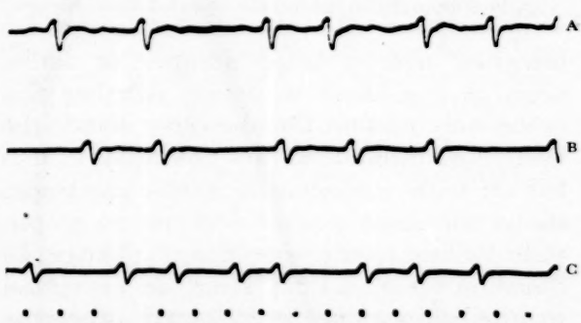


FIG. 5. Fatigue during maximal effort[3] action potentials led off from vastus medialis with concentric needle electrode (previous poliomyelitis). A, after 1 second, temperature 36.1°C. B, after 19 seconds, temperature 36.1°C. C, after 34 seconds, temperature 36.6°C. Distance between time marks 20 milliseconds.

individual spike decreases gradually with fatigue. (Fig. 4.)[18] These observations have been confirmed lately by Hodes[33]; the decrease in amplitude also occurs in the course of repetitive electrically-induced contractions. Prostigmine partially counteracts the abnormal electrical response. The effect is comparable with the gradual decrease in amplitude of action potentials in partial curarization or in myasthenia gravis,[31] and it therefore seems probable that it is connected with changes at the neuromuscu-

lar junction. According to Hodes[33] this effect should be due to the dropping out of some muscle fibers or whole motor units, i.e., a mechanism which also occurs in fatigue of normal muscle. When the leading off is done with surface electrodes, which

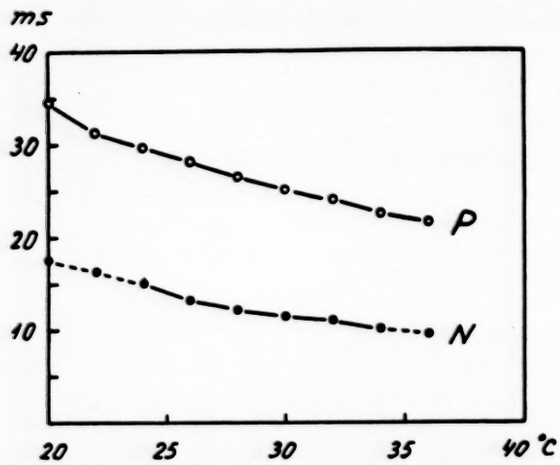


FIG. 6. Duration of action potential (ms) as function of intramuscular temperature in normal (n) and previously poliomyelitic (p) muscle.

integrate over a large number of active units, it is difficult to decide whether this is the only reason. On the other hand, the individual diphasic action potential, as it is led off with a concentric needle electrode, shows the same *gradual* decrease in amplitude without any significant change in duration. (Fig. 5.)[13,18] Thus, an exception to the all-or-none rule which otherwise determines the amplitude of action potentials in normal muscle fibers is suggested.

We have looked for further abnormalities in neuromuscular transmission. Compared with normal muscle, denervated muscle in most animals and in man has an increased sensitivity to intra-arterially applied acetylcholine.[17] Examinations of isolated muscle fibers reveal that even in denervated muscle this effect is due to a lowering of the threshold of a region in the fiber of high acetylcholine sensitivity which corresponds histologically with the nerve ending.[39] In poliomyelitis, even with a severe degree of paresis (i.e., denervation), neither the motor nor the vasomotor response to intra-arterial acetylcholine corresponds with those seen in denervation from other causes. Our preliminary results seem to indicate that the lowering of threshold is less marked than in, e.g., amyotrophic lateral sclerosis or peripheral denervation.

So far we have not been able to apply

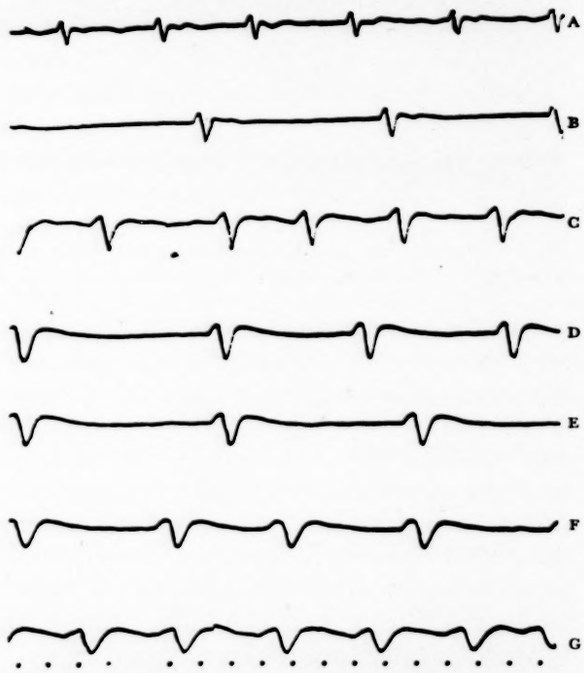


FIG. 7. Action potentials at decreasing intramuscular temperature in previously poliomyelitic muscle[3] led off with concentric needle electrode. A, 36.1°C.; B, 33.7°C.; C, 26.3°C.; D, 20.6°C.; E, 18.7°C.; F, 17.7°C.; G, 17.7°C. Distance between time marks 20 milliseconds.

these tests, except for the effect of fatigue, in the early stage of the disease; this applies also to comparisons of the duration, amplitude and shape of the individual spike potential with those found in normal muscle and in neurogenic atrophy of peripheral origin. However, the results obtained from observations in later stages of the disease may be worth mentioning in this connection.

In normal muscle the first phase (spike) of the diphasic action potential was found to last 4.6 milliseconds.* In poliomyelitis as in other cases of neurogenic atrophy the duration is considerably increased and values of 11.5 to 12.5 milliseconds were measured for the spike duration.[15] This

* Standard deviation 7.4 per cent, 245 measurements on sixteen different persons.

difference might be due to the 2 to 5°C. lower values of intramuscular temperature which are frequently present in poliomyelitis. But later investigations[3] have demonstrated that the temperature effect on the action potentials is identical in normal and poliomyelitic muscle (Fig. 6); in both, a decrease of 10°C. in the temperature range investigated results in an increase in the spike duration of 35 per cent, the action potential of poliomyelitic muscle having double the duration of that of normal muscle even when the two are compared at the same intramuscular temperature. In poliomyelitis the lower intramuscular temperature will cause a lower propagation velocity of the wave of excitation over the fiber and this difference may account for the difficulties encountered in the activation of poliomyelitic muscles at a low temperature. (Fig. 7.)

The amplitude of the action potential has a maximum at 25 to 30°C. in both normal and poliomyelitic muscles and in both, anoxia, investigated at a constant intramuscular temperature, causes a decrease in amplitude after 30 to 40 minutes. (Fig. 8.) In poliomyelitic muscle this decrease in amplitude is also accompanied by a decrease in duration of approximately 20 per cent. When fatigue is combined with either anoxia or low temperature, the two effects on the action potential are superimposed.

The abnormalities found in the electrical response thus clearly indicate that peripheral structures are involved in the pathologic physiology of the sequelae after poliomyelitis. Whether this involvement is the result of a direct action of the virus on the neuromuscular junction or is due to a secondary reaction following degenerative processes of a specific nature in the central nervous system remains an open question. For the time being the assumption of a secondary involvement appears more probable. An investigation of the effect of repetitive electrical stimulation in the acute stage might help to answer this question. Abnormalities, which at this stage of the disease are not yet apparent in voluntary contraction, might thereby be revealed.

It is my impression that the study of the pathologic physiology of autonomic disturbances in both the early and later

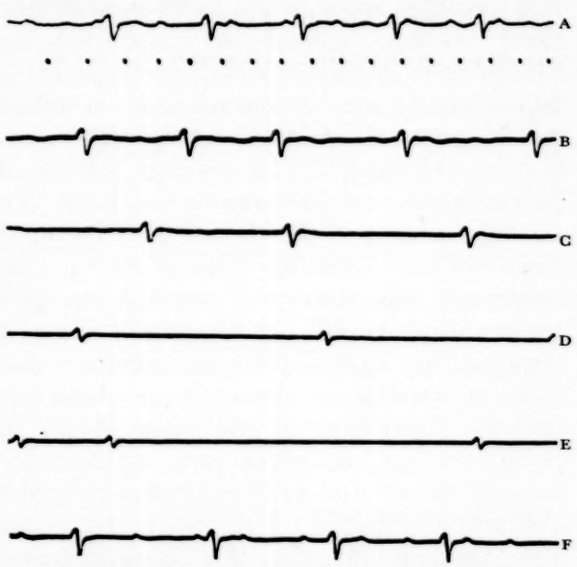


FIG. 8. Action potentials during anoxia[3] led off with concentric needle electrode, intramuscular temperature kept constant at 38.3 to 38.5°C. (previous poliomyelitis). A, 0 minutes; B, 37 minutes; C, 40 minutes; D, 44 minutes; E, 44.5 minutes; F, after eight-minute restitution. Distance between time marks 20 milliseconds.

stages of poliomyelitis has been rather neglected. Urinary bladder paresis which occurs in the acute phase has been previously discussed. In addition, abnormal reactions of skin temperature to indirect heating have also been described in severe cases in which bulbar involvement probably existed.[48] Normally, immersion of the lower extremities in water at a temperature of 42 to 44°C. causes a rise in the skin temperature of previously cooled fingers of about 10°C. The rise is abrupt and occurs after a latent period of 1.5 to 21.5 minutes, the rate of the rise being 3 degrees/minute.[21,30,42] Temperature changes in the skin are considered to be due to changes in the peripheral blood supply caused by changes in central vasomotor regulation, the tone of the vasomotor center reacting to small changes in blood temperature. In

a few cases of severe poliomyelitis the skin temperature of the fingers did not respond to indirect heating in the early phase of the disease but a normal response was observed later. Although it is not surprising to find disturbances in central vasomotor regulation in the early stage of poliomyelitis, these findings should be controlled by similar tests in patients with corresponding febrile signs and symptoms due to other causes before they can be accepted as conclusive evidence for a specific effect of poliomyelitis on autonomic activity. In the later stages of the disease and in slight cases without clinical signs of bulbar involvement no abnormal response in skin temperature could be recorded. Thus it remains an open question whether the signs of circulatory disturbances which are present, especially in the later stages of poliomyelitis, are secondary to the inactivity or are due to direct damage to the autonomic ganglia. The inactivity could also account for the low intramuscular temperature found in the paretic muscles. Although views with regard to the histologic evidence for damage to these ganglia are still somewhat conflicting, in monkeys the peripheral ganglia are definitely not specifically affected.[8] In man, damage was found in certain ganglia but the sympathetic chain usually escaped.[22] In patients with cervical cases the sympathetic centers in the lateral horns were found to be only rarely involved.[67] These observations are in agreement with the assumption that it is principally neurons with fibers of large diameter which are susceptible to virus.[34,55]

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Clinical Aspects of Acute Poliomyelitis*

DOROTHY M. HORSTMANN, M.D.
New Haven, Connecticut

THE older habit of classifying clinical forms of poliomyelitis according to elaborate schemes based on clinical evidence of the site of central nervous system involvement has fallen into disuse, and today a simpler, more workable classification is preferred. One which is in common usage and will be adopted in this paper designates *abortive*, *non-paralytic* and *paralytic* types, and fits various cases including spinal, bulbar and encephalitic into this framework. The *abortive* form is defined as a symptomatically non-specific, mild, brief illness without clinical evidence of CNS involvement; the *non-paralytic* as one in which clinical signs of CNS disturbance appear but nerve cell damage is not severe enough to produce weakness or paralysis; and the *paralytic* type in which definite muscle weakness or paralysis develops.

Since poliomyelitis is a common acute infection which only occasionally is associated with clinical evidence of CNS involvement, the abortive form of the disease is far more common than are the non-paralytic and paralytic types. Paul and Trask,[1] on the basis of house to house surveys carried out in 1931 and 1932, estimated the ratio of abortive to frank cases (non-paralytic and paralytic) to be about 9:1. Recently, however, evidence has appeared which makes it probable that the number of abortive cases has been underestimated, and they may outnumber the others by 20 to 1 as determined by Sweetnam in England,[2] or even several hundred to 1 as estimated in a recent epidemic in New Zealand.[3] The amount of virus calculated to be present in urban sewage from a large city when only a few definite cases were apparent[4] supports the latter figure, since it is likely that sewage virus is derived from unrecognized mild abortive cases as well as from asymptomatic carriers. In any event the cases in which paralysis occurs represents a small fraction of the total infections.

Abortive Poliomyelitis. Many, probably most, patients with abortive poliomyelitis are never seen by a physician and are not included in statistics of reported cases because no specific clinical diagnosis can be made. However, in spite of the fact that it is so non-specific an illness clinically, it seems likely that abortive poliomyelitis is sometimes, if not often, correlated with actual invasion of the central nervous system by the infective agent. An earlier concept that this brief febrile episode—sometimes termed a "minor illness"[5]—represents a systemic reaction to a generalized infection, preceding the central nervous system invasion or passage of the blood-brain barrier[6] is no longer tenable. At least in the experimental disease, as shown by Bodian and Howe,[7] scattered but at times extensive lesions are found in the central nervous system of chimpanzees with abortive or non-paralytic poliomyelitis following ingestion of infective material. In the human abortive disease *late* elevation of cerebrospinal fluid protein has been reported by Andelman and his associates.[8] This protein rise, appearing two or three weeks after the acute infection, may indicate that some pathologic process has been in progress in the central nervous system even though no clinical evidence of it appeared. It is possible, therefore, that asymptomatic human carriers or persons with symptoms of mild abortive poliomyelitis who are excreting

* From the Section of Preventive Medicine, Yale University School of Medicine, New Haven, Conn. Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

virus in their stools may also harbor it in their central nervous systems.

In any event, because of its epidemiologic and clinical implications the recognition or at least the appreciation of abortive as well as non-paralytic and paralytic poliomyelitis is of importance. The clinician's course with respect to the abortive disease is clear. Although these cases cannot be reported as poliomyelitis since a definite diagnosis is not possible, all patients with brief febrile illnesses during an epidemic should be regarded with suspicion and treated more cautiously than usual, for there is no way of telling which patients will go on to develop frank poliomyelitis. In the beginning the physician may prefer not even to mention the diagnosis as a possibility, for families are prone to be apprehensive to the point of hysteria during a poliomyelitis epidemic and anything which minimizes commotion is desirable.

Non-paralytic and Paralytic Cases. There are several familiar patterns which the acute illness may take in both paralytic and non-paralytic types. The so-called "dromedary" or diphasic form is characterized by a first phase which is indistinguishable from the minor illness constituting the whole disease in the abortive form. The first phase may be followed by a few days of well being before the second phase is ushered in with a recurrence of first phase symptoms plus evidence of central nervous system involvement. Sometimes first and second phases are partially superimposed. Another situation, and the more common one, is that in which the first phase is so mild as to be missed or does not occur at all, and the acute illness develops with the appearance of central nervous system signs, sometimes after a vague non-febrile prodrome of several days' duration. Occasionally the onset may be prolonged with as many as ten days or more of prodroma without fever.

These various clinical forms of poliomyelitis are in some instances sharply defined and fairly easy to identify. Often, however, they overlap and merge so that diagnosis is anything but easy. Nor is it always easy to decide whether to classify a case of non-paralytic or paralytic. For the question as to whether transient weakness of a few days' duration deserves the term paralysis is one on which physicians frequently disagree. Our practice is to designate those cases as paralytic poliomyelitis in which weakness or paralysis is demonstrable two weeks from the onset of second phase symptoms.

INCUBATION PERIOD

Since poliomyelitis has such a variable clinical pattern it is not surprising that the incubation period should appear to be variable, too. Figures varying from three to thirty-five days have been given[9] but the average time is usually taken to be ten days. Inasmuch as we do not know what constitutes adequate exposure to the virus or exactly what form (or forms) such exposure may take, it is not possible to measure the incubation period with any degree of accuracy. The difficulty is enhanced by the fact that some patients have the biphasic course mentioned above and clinicians have not been consistent in designating the first day of the disease, whether it be the onset of the first or second phase. We have always considered the incubation period to be the time between exposure and the onset of first-phase symptoms, if such occur, in which case it is likely to average less than ten days. If no first phase occurs, one must date the incubation period from exposure to the onset of symptoms which may be ten days or longer.

THE HISTORY

An exploration into the epidemiologic circumstances often provides more of a lead as to diagnosis than do the actual clinical findings. Thus in the summer and during an epidemic the occurrence of mild, perhaps even non-specific symptoms compatible with early poliomyelitis are more suggestive of that diagnosis than the same symptoms encountered in the winter or in non-epidemic times. The probability of

poliomyelitis is enhanced if the patient is a child or a young adult or a young pregnant woman; if there has been other similar illness in the family, particularly in the young children; or, if a definite case of poliomyelitis has occurred in the family.*

In eliciting the story of the onset of symptoms in a suspected case, particularly in a child, it is well to question specifically about a possible bout of *first-phase* symptoms, for often these are so mild as to be discounted by parents and their occurrence as long as a week before the appearance of more dramatic second-phase symptoms does not couple them with the latter in parents' minds. Listlessness, fever, headache, sore throat in the absence of an upper respiratory infection, anorexia, vomiting (rarely diarrhea), alone or in combination are the commonest symptoms in the first phase. Often they are of exceedingly short duration, a matter of a few hours; occasionally they last as long as two days but rarely more. The interval of well being before the onset of the second phase, if such occurs, varies from one to six or seven days, commonly three to four days.

The *second phase* (which more often occurs without an antecedent first phase) may appear abruptly or gradually over a period of several days. If the onset of symptoms is sudden, fever, headache and vomiting are most commonly encountered. The headache may be frontal, occipital or temporal; it is sometimes mild, often severe and bursting or pounding in type. A complaint of sore throat is not common as a second-phase symptom (although redness of the pharynx is the usual finding). Diarrhea has been described as a prominent feature in some epidemics but constipation seems to occur more often. These early symptoms are often accompanied or followed quickly by spontaneous pain in the extremities, both deep pain and hyperesthesias, and sometimes paresthesias. Soreness and stiffness of the neck and back are prominent early symptoms. The soreness of the neck is not always associated with the extensor muscle group: in some instances the flexors are painful, in which case the soreness is localized to the lateral neck, sometimes unilaterally, sometimes bilaterally. The soreness and stiffness of the back is usually present in the lumbar region but occurs also in the thoracic region and the patient then localizes it "between the shoulders." Severe lumbar back pain not associated with motion of the spine—in fact relieved by it—also occurs (especially in adults), as does severe abdominal pain which may be cramp-like or steady and involve any quadrant, although usually the lower ones. Flank pain (in the flank muscles) is sometimes mistaken for abdominal pain by the patient and the physician. Pain in the chest is more often localized to the lower part of the thorax; it may be deep pain aggravated by breathing and is commonly associated with hyperaesthesia and tenderness to pressure over the chest wall.

If the second-phase symptoms develop gradually as they frequently do in adults, they may do so over a period of several days or occasionally several weeks. Listlessness, slight and intermittent headache, anorexia, mild pains in the extremities, and again hyper- and paresthesias can occur before the onset of fever. Sometimes slight stiffness of the neck, back and hamstring muscles are present also for several days before the febrile period begins. This so-called "straggling" type of clinical picture may persist throughout the second phase, or the mild symptoms may suddenly be superseded by fever, vomiting, severe headache, peripheral pain and a sharp increase in stiffness of the neck and back.

Whether the onset of the second phase is sudden or gradual, a number of other

* There have been many observations on the familial epidemiology of poliomyelitis. Paul, Salinger and Trask[8] concluded that "minor illnesses" which probably represent abortive poliomyelitis are four to six times commoner in the familial associates of a known case than in control groups in which no case has been observed. Casey, Fishbein and Bundesen[13] have reported similar figures. Pearson et al.[11] and Wenner and Tanner[12] have isolated poliomyelitis virus from up to 80 per cent of the family contacts of known cases, and Zintek's study of a family epidemic[13] illustrates the possible high incidence of infection in a family group with only one (or two) obvious cases.

symptoms may be encountered. These include psychic reactions and transient changes in personality such as extreme irritability not associated with pain or hyperesthesia. The sensation has been described by patients as one of overpowering restlessness and hypersensitivity to external stimuli such as noise. Varying degrees of emotional instability and overreaction often accompany this agitation. The emotional lability sometimes persists far into convalescence. Not infrequently a brief period (one day or less) of irritability is followed by more persistent listlessness, lassitude and even drowsiness and coma. Convulsions are rare but do occur. Dizziness, which is not true vertigo but a lightheadedness is not an uncommon early symptom. Shaking chills are rare and more apt to occur in the bulbar form of the disease. Generalized tremulousness is also more common with bulbar poliomyelitis but occurs with other forms as well.*

In epidemic times, due to extensive publicity to acquaint parents with the symptoms of early poliomyelitis, physicians are more apt to be called to see patients before any weakness or paralysis develops. Because the early clinical picture can be so varied and even bizarre, the diagnosis may be suspected but not clear until the appearance of muscle stiffness and weakness. As long as fever persists one can expect paralysis to develop (or to extend). Weakness of an extremity is sometimes preceded by stiffness and twitching of the involved muscle groups but these may occur without subsequent paralysis. The story of falling when attempting to walk or sudden collapse of an extremity so that the patient falls to the floor unexpectedly is not uncommon. The patient may say that he then got up and walked off with no difficulty. A day later, however, the leg may be weak or paralyzed.

Although the onset of weakness or paralysis is common while fever is still present, it often occurs as the fever begins to fall and concurrently with an improvement in the general clinical picture: the patient feels more alert, his headache, back and neck soreness are much improved and his appetite begins to return. He feels on the road to recovery but suddenly discovers that his limbs will not function properly.

VARIABILITY OF SYMPTOMS IN DIFFERENT AGE GROUPS

As in many infectious diseases the influence of age on symptomatology is important. A recent survey of several hundred poliomyelitis patients in various age groups during two large epidemics*[14] has revealed that the clinical pattern in the non-paralytic and paralytic forms varies markedly in several respects with the age of the patient. Most striking differences were the following: (1) The diphasic, "dromedary" course was common in young children and rare in individuals over fifteen; (2) the onset of symptoms in young children was usually abrupt; in the older age groups it was often gradual and sometimes preceded by a relatively long prodromal period; (3) the time between the onset of preparalytic symptoms and the appearance of paralysis tended to be shorter in young children; (4) pain—both superficial and deep—was a more prominent feature of the disease in the older age groups than in young children.

The diphasic course, sometimes stated to occur in up to half the patients with signs of central nervous system involvement, diminished in frequency with increasing age of the patient as follows:

Age	No. of Cases	No. with Two Phases	Per cent with Two Phases
2–4	83	29	35
5–9	105	40	38
10–14	78	13	17
15–19	58	6	10
20+	59	7	12

Comparing combined age groups 2–4 and 5–9 with 15–19 and 20+, chi square = 24.14. P = <0.001.

* Since bulbar poliomyelitis is being discussed as a separate subject in this symposium, its special features will not be dealt with here.

* Detailed clinical histories were taken by one person from all the patients, or from the parents of the young children.

There was no striking preponderance of the diphasic course in the paralytic or non-paralytic groups.

Another difference was apparent in both paralytic and non-paralytic cases in the type of onset of "second"-phase symptoms, whether sudden or gradual:

Age	No. of Cases	Onset Sudden		Onset Gradual	
		No.	Per Cent	No.	Per Cent
2–4	83	70	82	13	18
5–9	105	86	82	19	18
10–14	78	44	56	34	44
15–19	58	27	47	31	53
20+	59	20	34	39	66

Comparing combined age groups 2–4 and 5–9 with 15–19 and 20+, chi square = 37.30. P = <0.001.

Spontaneous pain was encountered more frequently as the age of patients increased, and in individuals fifteen years and over it was striking. Severe, excruciating pain, sometimes as the first symptom and in the absence of fever, was a characteristic in the older age groups. This pain tended to appear suddenly during the night, most commonly in the low back but sometimes in the legs or flanks. In contrast to pain associated with stiffness of muscles it was relieved by motion and a number of patients told of having paced the floor all night in order to obtain relief. No counterpart of this type of pain was encountered in young children.

Age	No. of Cases	Pain as a Presenting Symptom*		Pain during First Twenty-four Hours of Symptoms†	
		No.	Per Cent	No.	Per Cent
2–4	83	27	33	33	40
5–9	105	41	39	58	46
10–14	78	24	31	41	40
15–19	58	33	57	44	76
20+	59	37	63	45	76

Comparing combined age groups 2–4 and 5–9 with 15–19 and 20+, chi square = 16.37* and 32.71† P = <0.001.

Tabulating all complaints of pain, either superficial or deep (exclusive of headache) occurring during the first twenty-four hours of symptoms, the figures in the preceding table were obtained.

In addition to being more frequent in individuals fifteen and over, peripheral pain was often severe and protracted in the older age group, and mild and fleeting in young children.

Some of the variations in symptomatology characteristic of children and adults are illustrated by the following two cases:

Childhood Type. B. D., a two year old girl, was well until January 19th when she complained of sore throat and was noted to be listless and anorexic. These symptoms plus a low grade fever persisted through the following day but on neither day was she ill enough to remain in bed. On January 21st all complaints had disappeared and she seemed entirely well although not quite as peppy as usual. She played actively, however, and had no complaints during the following two days. At 2:00 A.M. on January 23rd she awakened suddenly crying and complaining that her head hurt. She slept again but awakened in the morning screaming with severe headache. Her fever was high and she was nauseated and refused food. If allowed to lie still, she was quiet and uncomplaining through the day, but any slight movement seemed to aggravate the head pain. At no time was there a complaint of pain in the extremities. She was seen by a physician who noted a red throat and prescribed sulfadiazine. She spent a restless night, awakening frequently. By morning the fever was still high, the neck was stiff and she seemed unable or unwilling to move her extremities or raise her head. Complete paralysis of arms and legs was evident during the course of the day. After admission to the hospital paralyses of the intercostal muscles and diaphragm developed and respirator treatment was necessary for a three-week period. Convalescence was slow; there was some return of function in all extremities, but severe residual paralyses were present several months after the acute illness.

Adult Type. J. H., a twenty-six year old newspaper reporter, on September 19th began

to feel cross and irritable which was unusual for him. This continued for three days when he noticed in addition the presence of an area of hyperesthesia over the right side of his low back; the skin felt "as though it had been bruised" but inspection by a member of his family revealed no skin lesions. Irritability and hyperesthesia continued for three days unaccompanied by other symptoms until September 25th when he felt tired and listless on awakening and noticed a slight headache and slight backache. His temperature was normal and he did not feel ill enough to remain in bed. He spent an active day, retired early and slept well until 3:00 A.M. when he was awakened by an excruciatingly severe pain around the middle of his body, most severe in the flanks and low back. The pain was so severe that he could not remain in bed but got up and paced the floor, which seemed to give some relief. At 3:30 A.M. a physician was called. A diagnosis of probable ureteral stone was made and he was given morphine, which enabled him to sleep until 7:00 A.M. On awakening the pain was still severe and by afternoon there was in addition severe headache, nausea and vomiting, and slight stiffness of the neck. The temperature remained normal. Throughout the day there was extreme restlessness and the patient spent hours walking around, crying with pain, exhibiting an emotionalism which was most unusual for him. By 3:30 P.M. the back pain was so agonizing that the physician was again called, morphine was again administered, and the patient slept until 7:00 P.M. On awakening the same symptoms plus urinary retention were present, and hospitalization was recommended. The following morning, September 27th, a complete investigation of the genitourinary tract was undertaken but no ureteral stones were found. By afternoon the neck and back were stiffer and by the following day, September 28th, the legs were weak. A diagnosis of poliomyelitis was made and the patient was transferred to an isolation unit. At this time his temperature was 99°F., there was marked stiffness and retraction of the neck, marked stiffness of the back, and slight hamstring tightness, distended bladder, paralysis of both legs, weakness of the left arm, weakness of the intercostal muscles and diaphragm. Spinal puncture revealed 213 cells (84 per cent lymphocytes) and a + Pandy. He was placed in a respirator and on the following day, because of progressive bulbar signs, a tracheotomy was performed. His course continued stormy, with days of semicoma and cyanotic periods. After several weeks, there was improvement in the bulbar signs but

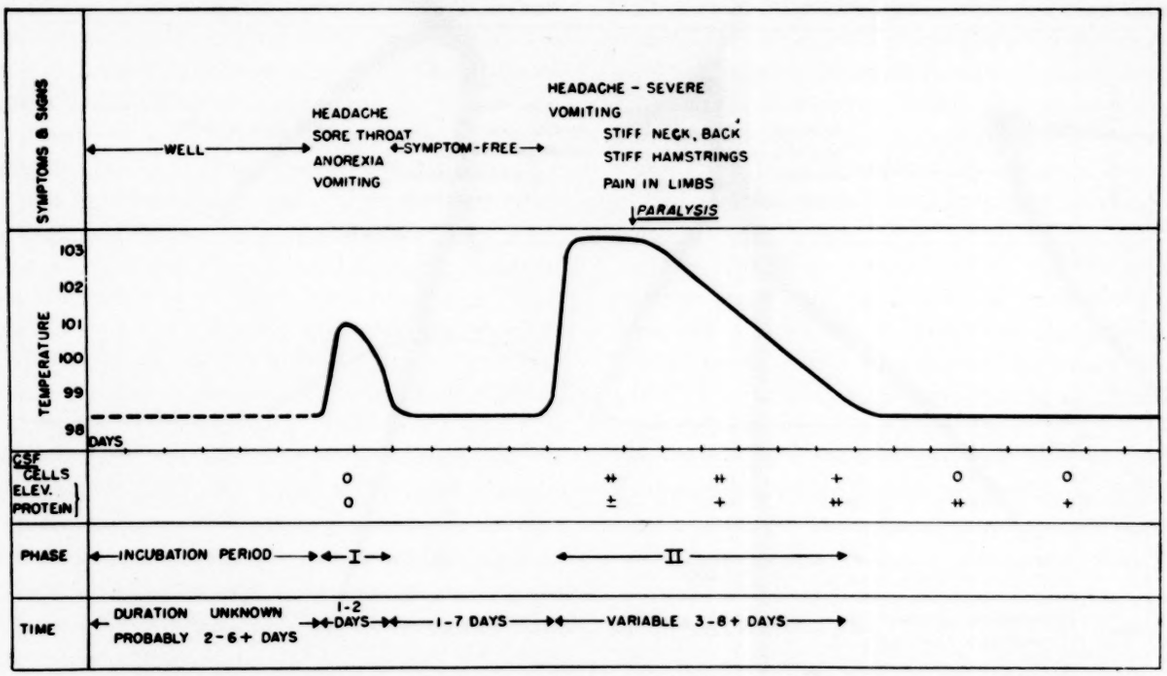

FIG. 1. Schematic diagram illustrating the clinical course of the "childhood type" of acute poliomyelitis.

the limbs remained essentially flail, and the patient was still in a respirator one month after onset.

Some of the differences in clinical pattern exhibited by these two patients are summarized in Figures 1 and 2. Young children (Fig. 1) often have a diphasic course, a sudden onset of the second phase and a short preparalytic period. Young adults (Fig. 2), on the other hand, have a single phase but a more prolonged illness with gradual onset, several days of prodromal pain and a long preparalytic period. These patterns are by no means rigid; some adults have courses similar to that described as the childhood type while children sometimes exhibit courses more characteristic for adults.

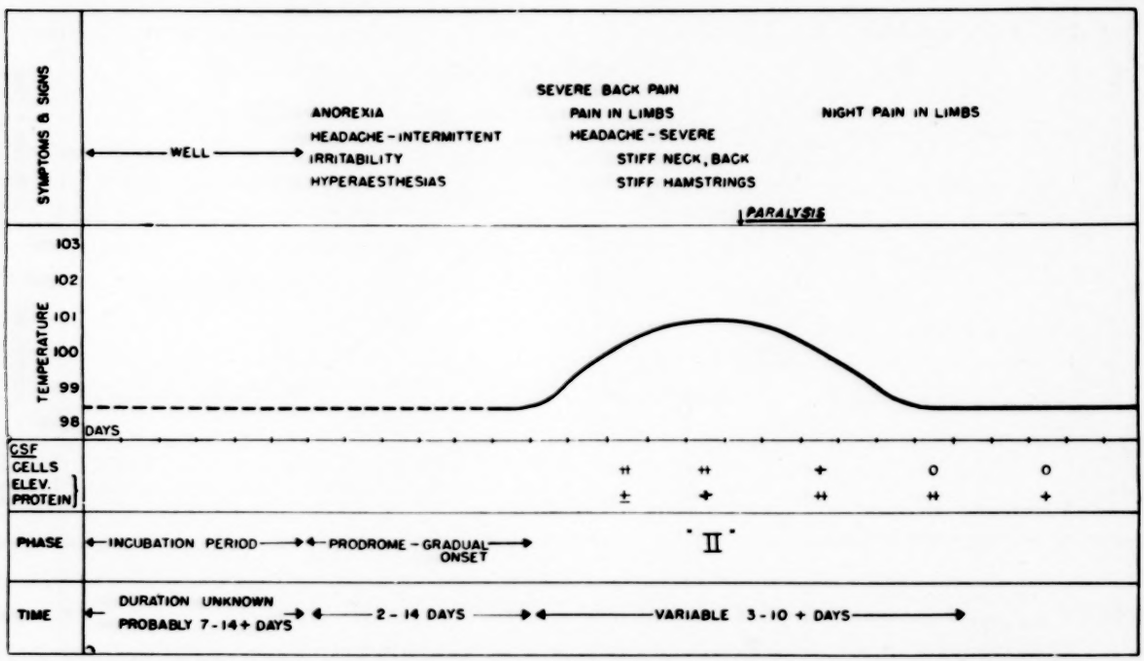

FIG. 2. Schematic diagram illustrating the clinical course of the "adult type" of acute poliomyelitis.

PHYSICAL EXAMINATION

The patient in the first phase, or the abortive disease, presents no abnormalities on physical examination except listlessness, fever and some redness of the pharynx. In the beginning of the second phase the situation is similar: there is fever, a dusky red appearance to the pharynx but little or no edema of the pharyngeal tissues. If and when the disease progresses, stiffness of the neck, back and hamstrings soon becomes very prominent and this condition is perhaps the most useful finding in establishing an early diagnosis. The stiffness may be mild, merely a slight resistance to the last degree of flexion of the neck, or it may, rarely, be so marked as to present opisthotonus. Stiffness of the spine is best elicited by having the patient sit up in bed with the knees naturally flexed and asking him to "kiss his knees." If the back is supple, this is easily accomplished without discomfort. If the back is stiff, however, it may be difficult or impossible to perform, and attempts to do so will be accompanied by considerable pain. In this case the spine sign is positive. If the back is flattened and rigid, the patient may not be able to sit naturally at all but will support himself on his two outstretched hands, his trunk tilted backwards, i.e., in the "tripod position" which is also a characteristic sign. Tightness of the hamstring muscles and resistance to extension of the leg are very common. Other muscles, including the calf

muscles and those of the upper extremities, may also exhibit stiffness and tightness; wherever this stiffness and tightness exist the muscles are apt to be sore and any attempted motion painful. The mechanism of the stiffness is not clearly understood, nor is it apparent why it persists undiminished in certain patients long after the acute illness has subsided, and sometimes in the absence of any muscular weakness.

Another sign which is perhaps less well known but was described at least thirty-five years ago[15] is "head drop." Dr. A. L. Hoyne, whose name is associated with this sign, has used it effectively and has emphasized its value. It is elicited by having the child lie on its back, placing one's hands beneath his shoulders and so lifting him up from the bed. In the normal child the head follows along in a plane with the body as it is raised but in poliomyelitis (even in its earliest stages) the head falls back limply in a position of hyperextension. Although this sign is not specific—it occurs in children severely ill with any prostrating disease including pneumonia and meningitis—in the obvious absence of such disease it is a useful sign which suggests poliomyelitis.

Although there may be stiffness of the back, neck and hamstrings, the reflexes in the early stages may be normal and active. In the non-paralytic disease they usually remain so. When changes begin to appear, characteristically there is first an irregular shift from normal to hyperactive, and then sudden (and sometimes transient) shifts to diminished or absent reflexes. Usually the appearance of reflex changes precedes the advent of weakness or paralysis by twelve to twenty-four hours, and may therefore herald that event. The superficial reflexes are the first to go: the abdominals, cremasteric and spinal reflexes. The latter, which are normally present segmentally from the upper back down to and including the gluteal region, although not so widely tested as the abdominals, are of similar significance; sometimes they disappear before the abdominals. The site of the absent superficial reflex is often of prognostic importance; thus if the right lower abdominal reflex disappears, one may expect to find some weakness of the right lower extremity the following day.

Changes in the deep reflexes have also a prognostic value. A diminished patellar response on one side, or an exaggerated one, may point to possible subsequent development of weakness on that side. As weakness and paralysis increase there is a progressive loss of reflexes, and a patient seen in the stage of severe paralysis of all extremities may have no demonstrable reflexes, superficial or deep.

The periodic examination for muscle power need not and should not be exhaustive in the acute stage of the disease but it is valuable to have a record of the general state of the muscle groups as a base line. All patients in whom there is progressing muscle weakness require observation frequently for evidence of diminished excursions of the intercostals and diaphragm.

CLINICAL LABORATORY FINDINGS

Spinal Fluid. The most valuable laboratory test in the diagnosis of poliomyelitis is the examination of the spinal fluid. If the total white cell count is elevated above 8 to 10 cells, and the protein above 35 to 45 mg. per 100 cc., the diagnosis in a suspicious case is more likely. Although spinal fluid abnormalities are usual in poliomyelitis, one cannot rely on a negative test to rule out the diagnosis, because if the patient has the abortive form or is in the first phase of a "dromedary" course, a negative spinal fluid is to be expected. If he has non-paralytic or even paralytic poliomyelitis, his spinal fluid may still be normal, especially if he is seen on the first day of symptoms. Occasional patients with the non-paralytic or paralytic form of the disease have persistently normal spinal fluid cell counts; in one series of cases the figure given was 12 per cent.[16] Fraser[17] cited a paralytic case which was fatal several hours after a spinal tap revealed a normal fluid and we also have seen a negative fluid in a fatal case proved at autopsy.

Although spinal fluid findings are not diagnostic (or prognostic) in poliomyelitis, certain features are characteristic at various stages of the disease. Since 1912[15] it has been emphasized that (1) the cell count is highest during the first week of the disease in the preparalytic and paralytic stages; (2) the predominant cell type is almost always the mononuclear although often early in the disease the polymorphonuclear form predominates; (3) the protein is low and often normal during the first week but rises during the second and third weeks, remains up through the fourth week, gradually decreasing to normal by the fourth to tenth week. Thus the protein is still elevated and often still rising while the cell count has returned to normal. Recent studies have confirmed and extended these early findings[18] and it is apparent that the CSF picture in *late* poliomyelitis resembles that of the Guillain-Barré syndrome and diphtheritic polyneuritis.

Blood. There is no consistent change in the blood picture. As a rule the white cell count is normal or moderately elevated (10 to 15,000) with a slight shift in the differential count and relative lymphopenia. If the patient is dehydrated, there may be a high hematocrit and a more elevated white cell count. Rapid erythrocyte sedimentation rates have recently been reported to occur in about half the patients tested.[19] At present there is no serologic test available which is diagnostic for poliomyelitis.

Urine. Routine urinalysis reveals no abnormalities. Watson and his colleagues[20] have described an increased excretion of coproporphyrin III in acute poliomyelitis.

DIFFERENTIAL DIAGNOSIS

During an epidemic certain diseases must be considered, especially in some areas. In the western part of the United States and particularly in California, the *arthropod-borne encephalitides* are the most important. Since the seasonal incidence and clinical picture of eastern and western equine encephalomyelitis and St. Louis encephalitis may be indistinguishable from that of poliomyelitis, the final diagnosis of these diseases rests on serologic evidence. Clinical signs which may be of help in differentiation include the greater tendency for patients with the encephalitides to show sustained high fever, convulsions, ophthalmoplegia, and less commonly than poliomyelitis, paralysis of the limbs.

Rocky Mountain spotted fever and *endemic typhus* are summer diseases (depending somewhat on the part of the United States and the time at which the vectors flourish) and can simulate the clinical picture of poliomyelitis. In their early stages fever, headache, severe muscle pain, hyperesthesias, restlessness, insomnia and stiff neck may all be present for several days before the rash appears to clarify the diagnosis.

It is now apparent that *mumps meningoencephalitis* may occur in the absence of parotitis, and may have a clinical picture similar to that of non-paralytic poliomyelitis. If this disease is suspected, it is important to ascertain whether classical mumps cases exist in the patient's family or community. There is no clinical sign which can be relied upon to differentiate aseptic meningitis from non-paralytic poliomyelitis, but both mumps and lymphocytic choriomeningitis can eventually be diagnosed by serologic means if acute and convalescent sera are available.

Mention has already been made of the patient with severe back pain whose illness is mistaken for kidney disease. Severe abdominal pain, which may shift from the epigastrium to the right lower quadrant and may be associated with nausea and vomiting, sometimes results in the admission of a poliomyelitis patient to a surgical service where appendicitis is suspected and an appendectomy may be performed before the correct diagnosis becomes apparent. *Epidemic pleurodynia* or Bornholm disease, which is also a summer disease, is occasionally mistaken for poliomyelitis; the rapid subsidence of fever and chest pain in twenty-four hours, without stiffness of muscles, distinguish it however.

The *Guillain-Barré syndrome* or infectious

polyneuritis seems to appear in the course of every epidemic of poliomyelitis. It should be entertained as a possibility in patients with paralysis whose spinal fluid *early* in the acute disease reveals a normal cell count but an elevated protein content. The clinical features which distinguish it from poliomyelitis are the symmetrical distribution of paralyses (particularly facial diplegia), the frequent occurrence of sensory loss and the absence of muscle tightness and pain.

Various infections including streptococcal sore throat, retropharyngeal abscess and the exanthemas are sometimes accompanied by transient meningismus which may be confusing. Other conditions which should be kept in mind and ruled out are the post-exanthem encephalitides, transverse myelitis, post-diphtheritic polyneuritis, purulent meningitis, tuberculous meningitis, as well as the more remote possibilities of rheumatic fever, trichinosis and osteomyelitis.

MEDICAL TREATMENT

At the present time there is no specific treatment available for poliomyelitis. None of the antibiotics or sulfonamide derivatives which have been tried has had any effect in destroying the virus or controlling its spread in the body. At one time it was believed that convalescent serum was a valuable specific form of therapy. However, no controlled trials have been reported which would support this view; in fact the recent study by Bahlke and Perkins,[21] in which large doses of gamma globulin were given to alternate patients in the preparalytic stage without demonstrable effect on their subsequent courses, establishes the ineffectiveness of such therapy as far as adult serum is concerned. Another point which militates against the use of serum is the evidence that patients may already have specific antibodies against their own strain of virus by the time they are admitted to the hospital.[22]

Since there are no specific therapeutic agents available, medical management comes down to general supportive measures and the anticipation and handling of complications.

Hospitalization. The tendency at present is to treat all patients in whom a definite diagnosis has been made in the hospital. This is probably wise since there is such uncertainty as to the future course in all early cases. However, the decision as to which cases are to be hospitalized and which may be treated at home will vary in different places and at different epidemics, depending on the local facilities available. A special isolation hospital is not necessary for general hospitals can care for poliomyelitis patients and should accept their community responsibility to do so. In the transportation of the patient to the hospital, care should be exerted that the trip involves a minimum of exertion and trauma.

In the hospital, management of the patient with poliomyelitis has become a task involving the services of a team of specialists. During the acute illness it has proved most satisfactory to have his care in the charge of the internist or pediatrician, with specialists in orthopedics and physical medicine acting as consultants, directing the special forms of treatment which are their province. Depending on the condition of the patient rather than on any arbitrary time designated as the end of the isolation period, the responsibility is transferred to the orthopedist or the specialist in physical medicine for convalescent and late treatment.

General Measures. Early bed rest is important for all patients whether at home or in the hospital. There seems little doubt that it is one of the most important therapeutic and preventive measures, especially after the onset of the preparalytic phase. Russell's recent study[23] suggests that there is a close correlation between the degree of physical activity in the early preparalytic phase and the final outcome in terms of severity of paralysis. Such correlation has long been postulated on the basis of clinical experience. The history of violent exercise immediately preceding the onset of paraly-

sis is not an uncommon one, and this fact coupled with experimental evidence that virus concentration in the anterior horn cells is high at least one day before paralysis appears[24] has been interpreted as indicating that physical activity may be one of the mechanisms which upsets host-virus equilibrium and precipitates irrevocable injury to the cells of the central nervous system. The evidence[23] that bed rest (i.e., avoidance of any physical activity) may be a factor which contributes to the arrest of the disease in the preparalytic phase is of great therapeutic importance. Bed rest for a few days following the abortive disease, and certainly a longer period following the mild non-paralytic type, is strongly recommended for rest may be one factor in preventing the late paralyses which sometimes occur.

Orthopedists recommend that a firm hard bed be provided from the beginning, particularly for patients with marked muscle tightness and paralyses. The bed should be fitted with a footboard placed several inches beyond the mattress end, allowing room for the heels or toes when the patient lies supine or prone. The footboard also serves to protect the extremities from the pressure of bed-clothing and allows proprioceptive reflexes to be stimulated when the feet rest against it. If the legs are weak, the knees should be supported in a slightly relaxed position; weak arms should be in external rotation alongside the body but not against it. If the patient is acutely ill or irrational, it will obviously not be possible to keep him in this position, but the sooner it can be achieved the better.

Purely medical aspects of treatment cannot of course be separated from other forms of therapy. The maintenance of good morale is an important feature which is apt to be overlooked in the stress of an epidemic when acute medical emergencies are at hand. Poliomyelitis, perhaps more than any other disease in our time, provokes fear and terror in the public mind. The patient whether child or adult, may therefore enter the hospital in a state of extreme apprehension. He requires continuous help and reassurance to enable him to adjust to his illness and perhaps to a permanent physical handicap. If this help can be given from the beginning, there is less danger of the later development of neurotic fears and dependencies which in addition to their psychiatric implications may interfere with the achievement of maximum physical improvement.[25]

Preparalytic Stage (and Non-paralytic Cases). In mild non-paralytic cases with little fever and minimal stiffness no treatment other than bed rest, light diet and adequate nursing care is necessary. In the more severely ill patient who has high fever and is dehydrated, parenteral fluids and salt are indicated.

Sedation and relief of pain are often pressing problems in the early acute disease. Relief of pain is best accomplished by the intermittent application of hot moist packs according to Miss Kenny's technic,[26] a subject which is reviewed in another article in this symposium. Hot baths may also be used effectively, especially in small children. Whenever hot packs or hot baths are used, salt tablets should be given to prevent chloride depletion which results from excessive salt loss in perspiration.

The response to the common analgesics is not very satisfactory but aspirin, codeine or demerol may be used. Often, if pain is relieved by means of hot packs and drugs, the patient will fall asleep easily and sedation will not be necessary. This is a desirable result for the danger of aggravating incipient or actual respiratory difficulty makes it necessary to use sedatives cautiously. Some physicians believe, however, that the relatively great physical activity of the restless, sleepless, patient tossing about the bed all day and all night represents a danger in possibly precipitating paralysis, and adequate sedation should therefore be given if there is no obvious respiratory embarrassment.

In recent years several drugs have been advocated for the relaxation of muscle tightness and relief of pain. Kabat and Knapp[27] introduced prostigmine in 1943 and it has received extensive clinical trial, with variable results.[28,29] Ransohoff[30] has

recommended curare enthusiastically but not all are agreed as to its benefits[31] and it has been found to be a drug of considerable potential danger. Cole[32] states that none of the drugs has been found to be as effective as the more tedious and cumbersome method of hot packs, and none has therefore come into general use.

Paralytic Stage. What has been said of the care indicated in the pre-paralytic phase applies equally to the early paralytic. The problem of the relief of pain may continue for some time. Although the patient is comfortable during the day, he may suffer *night pain*, severe, deep, aching pain in the weakened or paralyzed back or extremities, which persists sometimes for weeks. This pain often defies every form of treatment which may be tried, including continuous hot packs, analgesics and sedatives.

Complications. Certain complications require special treatment. *Urinary retention* is common in patients with severe involvement of the lower extremities. Before resorting to catheterization an adequate trial of drug therapy should be given. So far, the parasympatheticomimetic drug, furfuryl trimethylammonium iodide ("furmethide") has proved the most efficacious if given in adequate dosage.[33] If there is no response to drugs, catheterization will be necessary. It may be required for several days, in which case prophylactic sulfadiazine should be given. In most instances retention lasts only a few days and there is no further difficulty. For this reason an indwelling catheter is rarely indicated and never until after several days' trial of drugs and repeated catheterization have failed. The objection to an indwelling catheter is that it tends to prolong the period of retention and the eventual risk of infection is therefore increased.

Atony of the gastrointestinal tract is a common occurrence, especially in patients with paralysis of the lower extremities. Prostigmine in small doses produces contraction of the bowel and relief of abdominal distention and discomfort. The normal tone of the gastrointestinal musculature usually returns spontaneously within a few days.

Respiratory failure is the most serious complication in poliomyelitis. It may be of two types (1) central, which occurs in bulbar poliomyelitis and results from involvement of the respiratory center; and (2) peripheral, as a result of involvement of the segments controlling respiratory muscles, the intercostals and diaphragm. Both types may be seen in the same patient at the same time. The extremely complex mechanisms of respiratory dysfunction which result have been studied in detail by Elam and his associates.[34]

The treatment of respiratory failure of the central type is a problem in the management of bulbar poliomyelitis and is discussed elsewhere in this symposium. In following a patient with spinal poliomyelitis who is beginning to have difficulty in breathing it is wise to have a respirator at the bedside ready for use, for sudden changes in the character of the breathing may necessitate immediate artificial respiration. If there is doubt about the function of the diaphragm, fluoroscopy of the chest is helpful in determining its degree of motion. Not infrequently the first signs of trouble are due not to actual weakness of the respiratory muscles but predominantly to their being "in spasm," i.e., tight and stiff, just as other muscles may be. The first form of treatment to be tried, therefore, is hot moist packs to the chest, applied intermittently for twenty- to thirty-minute periods. In some instances the respiratory exchange (which can be followed easily by listening over the mouth or nose with a stethoscope) improves and the patient relaxes. In others, in whom progressive muscle weakness is occurring, there may be no improvement but a progression of symptoms and signs: more and more feeble respiratory excursions, increasingly rapid pulse, cyanosis and apprehension. In such a situation respirator treatment will be necessary.

Once in a respirator the patient requires constant attention. If he is severely ill or comatose, a Levine tube for feeding will be necessary. Intravenous fluids are frequently required. Sometimes considerable explana-

tion may be necessary before the patient can be persuaded to coordinate his breathing with the respirator and not to fight the machine. If there is some element of central respiratory failure as well as respiratory muscle paralysis, the respiratory center may be sending out irregular impulses which interfere with the rhythmical mechanical respirations induced by the respirator. In such instances curare has been employed to block the response of the respiratory muscles to the irregular stimuli issuing from the respiratory center, thus allowing the respirator to "take over." Usually it is necessary to give only one dose following a test dose, for once the respirator rhythm is established it continues reflexly.

From now on many possible complications may occur. It is useful to have a stethoscope taped over the P.M.I., the ear pieces extending to the outside, in order to record the heart rate at frequent intervals. Prophylactic penicillin may be given to protect against respiratory tract infection. Continuous intranasal oxygen is indicated if the color is poor or if there is any evidence of central respiratory failure. (If the patient has had a tracheotomy, oxygen is given through the tracheal tube.)

Pulmonary atelectasis is a complication to which respirator patients are particularly prone. It can be prevented to some extent by the use of oxygen under positive pressure either continuously or intermittently by mask. When atalectasis occurs, bronchoscopy and removal of the plug of secretions may be a life-saving measure. Not infrequently patients develop recurrent attacks of cyanosis but on bronchoscopy no plug is found. Patchy peripheral atalectasis is a possible explanation of these episodes; they may be difficult to control but positive pressure oxygen seems to reduce the frequency of their occurrence.

The problem of dispensing with the respirator as early as possible is important since the machine tends to suppress the normal mechanism of breathing, and the patient literally forgets how to breathe by himself. Also, the longer he is in a respiratory the more difficult the process of weaning him away from it becomes. The use of the oximeter, described by Millikan,[35] has proved of benefit in enabling clinicians to follow the progress of the patient with respect to his respiratory function. This instrument is attached to the pinna of the ear and readings of the relative saturation of oxyhemoglobin in arterial blood are obtained. The level can be followed when the patient is removed from the respirator, a fall below a certain level being an indication for him to be returned to the machine. Usually the time out of the respirator can be increased gradually, day by day, until the machine can be abandoned entirely.

PROGNOSIS

As far as the acute stage of poliomyelitis is concerned, the subject of prognosis can be summarized briefly: (1) Early in the course no prediction can be made. (2) As long as fever persists there is a possibility that paralysis may develop or extend; once the temperature has returned to normal the development of paralysis is rare. (3) The mortality rate varies considerably in different epidemics but is usually 5 to 8 per cent. It is greatest in the bulbar form of the disease and in those with peripheral respiratory failure. It varies also with increasing age of the patient, being considerably higher in adults than in children.

CLINICAL IMMUNITY

It has usually been assumed that one attack of poliomyelitis confers solid immunity to the disease. There is evidence that chimpanzees, who seem to resemble humans in their response to infection with the virus of poliomyelitis, can be infected repeatedly with different strains of virus but are not subject to reinfection with the same strain.[36] In the human disease authenticated second attacks have been reported rarely but they probably occur more often than they are reported. Fischer and Stillerman[37] have raised the question as to whether the low morbidity rate in poliomyelitis would not make the incidence of second attacks rare even if no immunity occurred following the disease. In the 1935

New York City epidemic they observed four second attacks, a rate of 2 per thousand, which was within the limits of expectancy if no immunity resulted from a previous attack. However, these figures were not based on age specific rates and cannot therefore be taken as final. Nevertheless, increasing evidence of the widespread distribution of virus during epidemics suggests that reinfection with poliomyelitis virus may occur more often than has been supposed, but the reinfection usually remains at the subclinical level.

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Moist Heat in the Treatment of Poliomyelitis*

WILLIAM T. GREEN, M.D. *and* THOMAS GUCKER, III, M.D.
Boston, Massachusetts

MOIST and dry heat have apparently been advocated for the treatment of poliomyelitis from the time the disease has been recognized. Recently the use of hot packs has been so emphasized that they have in the popular mind come to indicate a method of treatment from which miraculous effects are to be expected. In truth they have no such effects although the use of moist heat and hot packs represents an adjunct which is distinctly helpful.

Treatment in poliomyelitis is adjusted to the problem presented by the individual patient and to the stages of the disease, whether in reference to the use of moist heat or other factors. For our purposes the disease may be classified as follows: (1) The acute stage which represents the febrile illness; (2) the convalescent stage which follows the acute illness and may be said in a general way to start forty-eight hours after the febrile illness and extend for approximately sixteen months and (3) the chronic stage. The convalescent stage may be subdivided into: (1) the sensitive phase when muscle sensitivity and spasm are present and (2) the asensitive phase when significant sensitivity and spasm have disappeared.

This discussion of moist heat primarily will be concerned with its use during the latter part of the acute illness and the sensitive phase of the convalescent stage.

PROBLEMS PRESENTED BY THE DISEASE

Before discussing the place of moist heat in treatment it is well to consider some of the manifestations of the disease and certain of the objectives of treatment. In the paralytic phase of the acute stage and in the sensitive portion of the convalescent stage the disease tends to be especially crippling and deforming since the findings are those of a combination of flaccid paralysis and of sensitivity and spasm of the muscles. This combination tends to be particularly deforming, in that the paralyzed muscles cannot control the part and the muscles which are in spasm tend to draw the part into deformity. Gravity often accentuates these bad positions. Since the muscles are sensitive to stretching and handling, the deformed positions tend to be maintained unless counter measures are taken. As time goes on these deformities become fixed due to secondary adaptation of the muscles to their shortened length. The longer a part is left in a fixed attitude the more difficult it is to get it out of this position. Very similar phenomena were demonstrated experimentally in animals by Ranson and Sams[1] as a fundamental neurologic mechanism occurring in conditions other than poliomyelitis. They proposed the term "hypertonic contracture" to describe the state of muscle spasm and applied the term "myostatic contracture" to the secondary shortening of the muscles.

Patients show great variability in the degree of sensitivity and spasm, as do the individual muscles in the same patient. Certain muscle groups are more likely to show spasm of a significant clinical degree than others. Particularly is this true of the posterior muscles of the neck, back, thigh and calf and the adductor muscles of the arm. Those muscles which would show spasm as a result of meningeal irritation from any cause are ordinarily the first to show spasm in poliomyelitis. Furthermore, it is noteworthy that the pain and sensitivity

* From the Harvard Medical School, and The Orthopedic Dept., The Children's Medical Center, Boston, Mass.

frequently do not parallel the amount of demonstrable spasm. Those patients with severe pain and sensitivity do not necessarily have more tightness of muscles than others. The duration of the sensitivity varies widely. Sometimes significant spasm and sensitivity are minimal after a few days. More often it exists for two to three weeks and occasionally it is present for a much longer period. In part at least this duration has a specificity for the individual patient.

Although the cause of paralysis in poliomyelitis is well accepted the explanation of pain and spasm remains controversial. Years ago involvement of the posterior ganglia was considered to be a likely cause.[2] More recently pathologic studies[3] have led to the proposal of an hypothesis that the spasm is due to involvement of the internuncial cells in the spinal cord. Still others[4,5] have suggested that involvement of the reticular formation and vestibular nuclei in the brainstem may give rise to muscle spasm.

Actually many of the phenomena in the general field of pain are imperfectly understood. The reaction in an individual which is described as pain can be elicited by numerous agents and conditions through a complex physiologic and psychologic mechanism. Studies[6] of the factors involved in the production of pain in contracting skeletal muscle, particularly in angina pectoris and intermittent claudication, have suggested the presence of a chemical substance which others[7] have concluded is related to lactic acid produced in the metabolism of muscle. This presumably stimulates pain receptors when it reaches sufficient concentration. Ischemia, through vasoconstriction, favors the concentration of such a substance and vasodilatation alleviates pain by an increase in blood flow which reduces the concentration. The relation of pain in poliomyelitis to ischemia of the muscles has been proposed[8] but recent studies by Gucker, Green and Anderson[9] of the skin and calf muscle temperatures in paralyzed and unparalyzed extremities of patients in the early stage of poliomyelitis have demonstrated that there is no primary vasoconstriction as determined by this method. Little evidence exists to substantiate a chemical substance theory in explaining the pain and sensitivity of acute poliomyelitis. Clinically, the "spasm" seems to be, at least, very similar to so-called reflex muscle spasm which accompanies pain arising in such conditions as peritoneal irritation, inflammation of joints and fractures.

Whatever their pathogenesis the pain, muscle sensitivity and spasm are significant factors in the disease although the prognosis depends essentially upon the degree and distribution of the paralysis. If there is no detectable paralysis, the spasm and sensitiveness are of little consequence except to make the patient more or less comfortable. However, sensitivity and spasm in a patient who has paralysis contribute to deformity, impair muscle function during the sensitive stage and upset reciprocal innervation. Deformities not only disturb function through mechanical abnormality but inhibit the recovery and function of muscles which are maintained in the stretched position. Furthermore, in the growing child deformities once established are often progressive.

It is not within the scope of this article to discuss the general problem of therapy in poliomyelitis. It is our purpose to consider only those aspects which are related to the use of moist heat. Some of the objectives of therapy are the relief of pain, prevention and correction of deformities and development of full ranges of motion as early as this can be done comfortably. It is in this sphere that the use of moist heat seems to be helpful since there is no evidence that its use affects the degree of paralysis.

PHYSIOLOGIC ACTION OF MOIST HEAT

The soothing effect of heat upon pain from various causes is well known. In a painful joint with muscle spasm heat is of assistance in relieving the pain, reducing spasm and promoting motion. The exact

mechanism by which heat accomplishes this is not certain.

According to Krusen,[10] extremely hot or cold water increases the sensitivity of cutaneous nerve endings whereas prolonged warm or cool baths diminish sensibility and relieve pain. A warm bath is more effective and acts as a depressant. Bazett[11] states that the superficial capillaries, venules and arterioles dilate in response to heat, resulting in an increase in the rate of blood flow which intensifies the thermal conductivity of the tissues. This increased circulation tends to distribute the heat throughout the body thus hindering a rise in the local temperature. Significant heating of the deeper tissues occurs in the specific area to which the heat is applied. Application of local heat elevates the temperature of the muscle to a very considerable degree.[12] One of us (T. G.) has shown that this is accomplished whether hot packs, luminous heat or tubs are used. With hot packs, the rise in skin temperature is abrupt whereas with luminous heat it is more gradual. Comparable increases in the deep muscle temperature occur, however, by both methods.

If a pack at a temperature as high as can be comfortably tolerated is applied to the lower leg of a patient in a room of ordinary temperature, there is usually a rise of 6 to 10°F. in the gastrocnemius, with 98 or 99°F. being the average temperature of the muscle. Furthermore, after the pack is removed and the bed clothes are replaced the muscle maintains this elevation and its increased circulation for some period. There is little drop during the first hour and only a small amount at the end of two hours. After three hours the temperature of the muscle approaches the temperature which existed prior to the application of heat.[13] Barcroft and Edholm[14] have correlated changes in muscle temperature with the blood flow in the forearm of normal subjects. They found that the flow is almost doubled when muscle temperatures are elevated from 89.6 to 95°F. This was a usual initial response. Furthermore, these observers have brought forth good evidence that the increased blood flow occurs equally in muscle and skin under these conditions.[15] It is known that the application of local heat does raise the temperature of the muscles and increases its blood flow. Whether these actions alone account for the greater part of the effect of the local heat is not certain. At any rate it is a fairly general observation that locally applied moist heat is helpful in relieving pain in poliomyelitis and its use in various forms preliminary to physical therapy seems to aid in developing ranges of motion and in correcting deforming attitudes. Watkins,[16] however, using the total voltage of electrical potentials contributed by a particular muscle during a standardized stretching period as an index of spasm, concluded that a twenty-minute application of the Kenny type of hot pack was without significant effect as evaluated by this method. This technic, however, does not necessarily represent an evaluation of the clinical manifestation of spasm. Certain others[17] observing a limited number of patients concluded that hot foments have no clearcut effect in aiding the return of normal ranges of motion. Heat does, however, seem to reduce the irritability and properly used has come to occupy a respected place in therapy.

METHODS OF APPLYING MOIST HEAT

Hot Packs. The first specific reference to hot packs with which we are familiar was made by Bradford, Lovett, Brackett, Thorndike, Soutter and Osgood[18] in 1909. They stated that, "The application of heat, either as warm, moist or dry packs . . . will often be found to relieve pain." Subsequently, Legg[19] and others included hot packs as an adjunct to relieve the sensitiveness and to facilitate the performance of muscle re-education and the maintenance of full joint mobility.

Numerous types of foments have been advocated. Many have placed great emphasis upon the details of their application and certain routines have been recom-

mended which involve frequent intensive packing for each patient and require extensive personnel. Two general types of packs are in current use: one may be called the "wrap-around pack" and the other the "lay-on pack." Since the recommendations of Kenny,[20] woolen cloth has come to be the favored material for use and it does have certain advantages. Both types of packs follow the general plan of application directly to the skin of the hot, wet wool from which the water has been well wrung. This pack is then covered by two additional layers, one of a waterproof material and the second of other material which is applied for additional insulation.

The Kenny pack is a wrap-around type of pack and its preparation and use has been described in detail elsewhere.[20] The materials used in the pack are of three shapes, square, rectangular and triangular, depending upon the part to be covered. The inner portion, composed of two layers of wool flannel, is taken directly from boiling water, is run through a wringer twice and immediately wrapped about the part smoothly and firmly. The pack is as hot as the patient can tolerate. Around this inner pack is wrapped a layer of waterproof material of similar shape, a single layer of dry flannel and finally an outer layer of cotton flannel or terry cloth which is pinned in position. Kenny recommends that essentially all parts of the body and extremities should be packed except the major joints which should not be covered in order that there be no restriction of motion. This entails many individual packs. In the acute stage the packs are described as being renewed every hour for twelve hours per day. During the convalescent stage they are renewed every two hours during the day until all signs of spasm and tightness have disappeared. This is mentioned as usually requiring six or eight weeks but may continue for many months. If the spasm is severe, and on special indications, the packs may be applied more frequently and at night.

Such application of packs makes a tremendous demand upon personnel. In practice many modifications of this technic have evolved. These variables include methods of applying the packs, the frequency with which they are applied and the areas which are covered.

The lay-on type of pack is more simple and rapid in its application. As its name implies it is laid in position over the part. It is more frequently used with the patient in the prone position to cover the neck, back, shoulder girdle, buttocks, thighs and calves although this type may be used in any area. For the packing in a prone position usually one pack rectangular in shape is used to cover the trunk from the occiput to the gluteal fold, and two other rectangular packs are applied to each lower extremity extending from the buttocks to include the heel and foot. Usually they are applied only to those areas which are most sensitive.

Circumstances and the availability of equipment and materials often determine the type and method of applying hot foments. For specific details and means of improvising equipment the reader is referred to two summaries of nursing care for poliomyelitis patients.[21,22] Commercial machines which deliver the packs heated and of the desired water content are available and simplify their application.

In our experience Munsingwear in four thicknesses has been found to be a very satisfactory and economical material for the inner portion of the pack. Koroseal has proven to be a serviceable water-proof material and a covering layer of wool cloth is used for additional insulation. The four thicknesses of Munsingwear constituting the inner layer are stitched together around their edges and diagonally. The Koroseal and outer wool covering are sewn together along their edges. Thus the application is simplified by having what amounts to two layers to apply rather than three or four.

Hot packs should be used for specific purposes. They may well be omitted in a patient with little sensitivity or spasm and they should be employed only in those areas

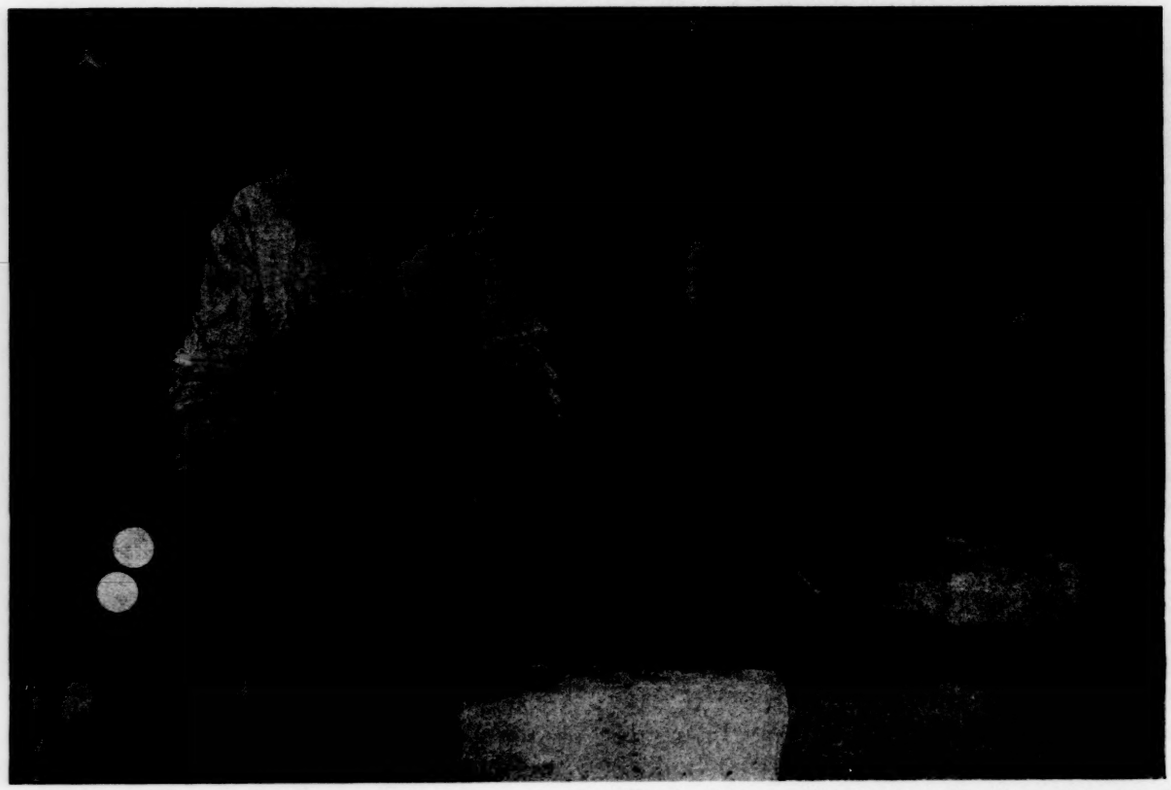

FIG. 1. "Lay-on" type of pack as used in the prone position. The hot inner pack is in place; the outer water-proof and insulating layer is about to be carried up over the trunk. Note that the pack is carefully tucked under and about parts.

in which sufficient sensitivity exists to indicate their use. In practice the lay-on packs are adequate for most patients. When patients are in a prone position, such packs can be applied to cover the greater part of the body with direct application to the areas which often are most sensitive. If the pack is carefully tucked around under the shoulders, trunk, hips and around the sides of the thigh and legs, a greater part of the surface is covered. In very sensitive patients the lay-on rather than the wrap-around pack is almost a necessity in order not to cause the patient more discomfort by the additional handling necessary to their application. (Fig. 1.)

In general, continuous packing is not recommended. It tends to be debilitating and we do not believe it has any particular advantage. If such packing is performed, adequate fluid intake and urinary output must be maintained. During the febrile period additional sodium chloride should be given.

The technic which we usually follow is that of using the lay-on pack over a period of approximately thirty minutes. The packing is repeated once during this time. As a rule three or four packing periods of thirty minutes each, distributed at four- to six-hourly intervals during the day and evening suffice. Often only two or three packs are used and then only to areas where they are indicated. Night packs should be used if the patient is awake and uncomfortable but never should he be awakened for their application. Packs seldom need repetition within three hours. As Gucker has shown the temperature of the muscle is raised very definitely by a twenty-minute pack and this elevated temperature is maintained for two to three hours. Occasionally more frequent selective packing of an area may be used if there is spasm

of the intercostal muscles and accompanying respiratory embarrassment. When the sensitivity is extensive, the wrap-around packs may be used in particular areas. If it is concluded that packs are indicated, the areas which are covered and the frequency with which the packs are employed should be geared to the individual patient. Observation of his subjective and objective reactions to the packs are of assistance in decisions regarding their use.

Hot packs have particular value preliminary to physiotherapeutic measures. The heat tends to relax tight structures and allows greater ranges of motion to be developed without provoking pain. As soon as the acute illness is over gentle passive motion to correct deforming tendencies and to increase range of motion should be employed after use of the packs. Ordinarily physical therapy should immediately follow the packs or at least it should be carried out within one hour after they are removed in order to take advantage of the increased relaxation and circulation. Preliminary heating, furthermore, seems to facilitate active exercises especially during the sensitive and early asensitive portions of the convalescent stage. It is our custom to provide physical therapy twice daily in addition to careful changing of positions by the nursing staff.

Some patients do not tolerate hot packs well and if they do not seem to be of value they should be discontinued. Particularly when they are first given, the packs should never be so hot as to cause discomfort. Occasionally the skin is irritated by the wool. Such patients generally tolerate heat given by immersion in a warm bath or tub, especially if the water temperature is raised gradually rather than being too hot at the start. No magical effect upon the disease process arises from the use of hot packs. Other measures are more important in the care of patients with poliomyelitis but moist heat is helpful in arriving at certain objectives.[23,24]

Warm Baths. Heine[25] in 1840 first commented on the use of warm and steam baths in the treatment of poliomyelitis. Subsequently, Wickman,[26] Lovett,[27] Lowman[28,29] and Legg[30] described the use of baths and underwater therapy for the disease's various stages. Since 1928 the tub developed by Mr. Carl Hubbard has been used extensively.[31] This tub is particularly shaped to facilitate handling of the patients during their period of exercise. (Fig. 2.)

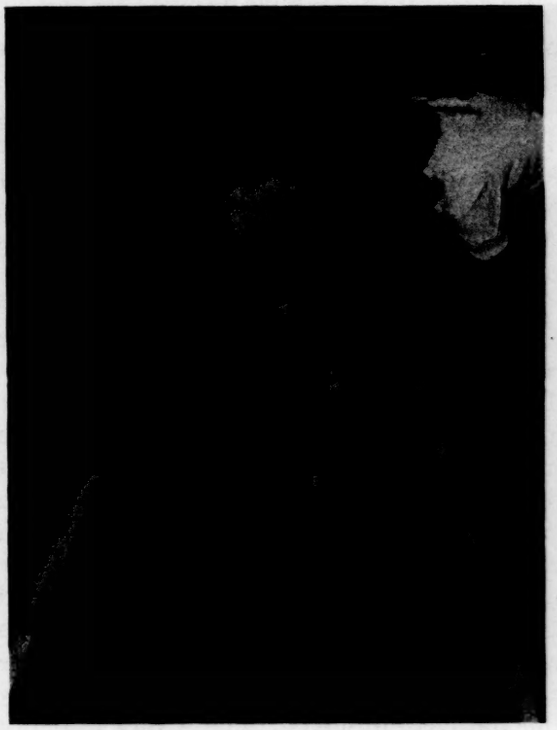

FIG. 2. The Hubbard tub. The patient is transferred to the tub without eliciting pain. The water is usually between 98 and 101°F. The warm bath relieves pain, allays muscle sensitivity and spasm and permits ranges of motion and other desired maneuvers to be accomplished more freely and with less discomfort.

The warm bath is an excellent way to apply moist heat. It may be employed as soon as the acute illness is over providing that the facilities and technics for handling the patient are such that he can be placed in the tub without provoking pain or trauma. In many places use of the bath is deferred until two weeks after the onset, which is a common period for quarantine. The water should not be uncomfortably

hot and ordinarily should be somewhere between 98 and 101°F. Occasionally water of slightly higher temperatures up to 104°F. is not uncomfortable for certain individuals. The patient ordinarily should not be left in the tub for longer than twenty minutes in order to avoid enervating effects. A longer or a shorter time may be appropriate for the individual patient.

The warm bath soothes pain and sensitivity and relaxes the muscles. Exercises are performed while the patient is in the tub. The relaxing effect on the tight muscles allows a greater range of comfortable motion. The parts are gently carried out of deforming attitudes and ranges of motion can be developed more comfortably and easily. In addition, the buoyancy of the water and the warmth permit the weakened muscles to perform more effectively. In motion of large parts the therapist can more easily control the movements. Frequently the bath is employed once a day and hot packs are given to particular areas at other times. The bath is especially indicated in patients who have extensive involvement. It is not within the province of this discussion to consider the general field of underwater exercises.

SUMMARY

The value of the hot pack has been exaggerated by many. Use of moist heat is a helpful adjunct in therapy but many other features of treatment are more important. There is no evidence that extensive, continuous packing should be practiced in poliomyelitis. Moderate use of packs seems to be helpful. Local heat applied for twenty minutes does raise the temperature of subjacent muscles to a significant degree for a period of two to three hours. Hot packs and baths tend to relieve pain, assist in making patients more comfortable and promote relaxation of tight muscles. Their use is particularly valuable immediately preceding physiotherapeutic measures which are designed to correct deforming tendencies and increase ranges of motion. Moist heat of itself will not accomplish these objectives. The hot bath, particularly as it can be given in the Hubbard tub, is to be commended.

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Bulbar Poliomyelitis*

Its Mechanism and Treatment

A. B. Baker, M.D.

Minneapolis, Minnesota

In spite of extensive studies on poliomyelitis, particularly during the past few years, very few publications have been devoted exclusively to the subject of the bulbar involvement in this disease. It is this latter form of the illness, however, that produces most of the fatalities and normally should warrant the attention and energetic investigation of the profession. For years there seems to have developed a fatalistic attitude regarding bulbar poliomyelitis—an attitude that is an admission of lack of understanding of the underlying mechanisms producing the various clinical manifestations and inability to cope with them. Recent advances in the fields of neuroanatomy, neuropathology and neurophysiology make it both possible and advisable to re-examine the problem of the cause of death in bulbar poliomyelitis in the light of this new knowledge, with further efforts being directed at more intelligently combating this disease.

One of the chief difficulties in studying this illness in detail has been the infrequency with which a large number of critically ill patients have been available to the same investigator within a relatively short period of time. During the 1946 epidemic in Minnesota such an opportunity became available to us. Within a four-month period 183 cases of bulbar poliomyelitis were admitted to the University Hospital alone. This large number of cases afforded us an opportunity of viewing this illness in all its clinical manifestations. It also offered an opportunity to study the effectiveness of various therapies and to investigate the pathologic physiology of this disease.

Generally, bulbar poliomyelitis has been considered clinically as a single disease entity in spite of a most diverse and widespread symptomatology. This attitude has retarded our progress and understanding of this illness. From our studies it is apparent that adequately to understand and treat this illness, it must be broken down into different groups, each with a predominant pathology and symptomatology. It must be emphasized that the various groups do merge into each other and rarely occur in pure form; however, such a classification does make for a more rational and intelligent approach to this illness.

GROUP I: CRANIAL NERVE INVOLVEMENT

In this group both the clinical symptoms and the pathologic lesions are limited to the nuclei of the cranial nerves. The brainstem reveals a mild inflammatory reaction consisting of both diffuse and perivascular mononuclears intermixed with numerous polymorphonuclears. The nerve cells show a patchy swelling and chromatolysis. The degree of neuronal damage is most variable from case to case, in some being very mild while in others destroying complete cell groups.

The clinical manifestations are generally correlated with the cranial nerve damage. Isolated ocular palsies such as ptosis and squints, total external ophthalmoplegias as well as pupillary disturbances may occur due to partial or complete involvement of the third nerve nuclei. Such ocular manifestations were not common in the patients at the University Hospital; they occurred in but 11 per cent. Disturbances of mastica-

* From the Division of Neurology, University of Minnesota Medical School, Minneapolis, Minn. Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

tion result from damage to the motor division of the fifth cranial nerve. Such palsies may be unilateral or bilateral and may implicate part or all of the muscles supplied by the fifth nerve. In unilateral lesions the jaw may deviate spontaneously when the patient opens his mouth, while at times the action of the pterygoid muscles must be tested by sideward deviation of the jaw against resistance. In isolated cases the patient may develop an acute severe trismus due to irritation of the fifth nerve nucleus. This may be a serious complication since inability to open the mouth prevents adequate removal of the secretions and may result in obstruction of the airway. We have observed this unusual complication in three patients. In such cases immediate tracheotomy is often necessary to prevent airway obstruction by secretions.

Paralysis or paresis of the facial nerve is observed fairly frequently in bulbar poliomyelitis and occurred in 53 per cent of our patients. In some cases the whole distribution of the facial nerve is involved; in others only one branch may be involved, such as that which supplies the cheek, the forehead or the lips; finally in still others the involvement is patchy, implicating one group of facial muscles on one side of the face and another set on the opposite side.

Bilateral deafness and vestibular disturbances may occur. Nystagmus was observed in several of our patients.

Involvement of these upper cranial nerve nuclei generally holds no threat to the life of the patient may be annoying and may result in residuals which can produce definite handicaps. They are of importance nevertheless because they should make the physician alert to the possibility of implication of more vital centers.

By far the most frequent cranial nerve involved in bulbar poliomyelitis is the tenth. These patients develop a weakness or paralysis of the soft palate, the pharynx and vocal cords. Their initial complaint often is a nasal twang to the voice, hoarseness, increased accumulation of secretions in the oropharynx or difficulty in swallowing. On examination there is generally pooling of saliva in the throat, the patient being unable to handle his secretions by swallowing. The speech has a nasal quality and may be hoarse from faulty innervation of the vocal cords. An occasional patient is unable to talk. Laryngeal stridor may be present. Weakness of the tongue may be bilateral or unilateral and may impair movement of food through the mouth and impede expectoration of saliva.

Considerable importance must be placed on lesions of the tenth cranial nerve because this nerve in conjunction with the eleventh and twelfth is essential for consummation of the act of swallowing. With inability to swallow there is the constant tendency toward pooling of saliva and food in the pharynx. This accumulation produces obstruction to the airway. A further threat to the airway results from the aspiration of fluid into the larynx or from reflex spasm of the glottis.

Interference with the airway should be combated by postural drainage and/or suction. However, in our experience it frequently has proved impossible to maintain an open airway by such measures even when constant suction is applied. When such procedures fail, tracheotomy should be resorted to immediately. Maintaining an unobstructed airway is of extreme importance in the care of these patients since any period of hypoxia, whether acute or chronic, can do irreparable damage to nerve cells already injured by the inflammatory process. Early evidence of such hypoxia generally consists of restlessness, apprehension, sleeplessness and increasing pulse rate and respiratory effort. The appearance of these latter symptoms in patients with lower cranial nerve involvement should immediately stimulate one to investigate those factors that might produce obstruction: (1) pooling of secretions due to paretic throat muscles; (2) paralysis of the tongue; (3) obstructed airway due to reflex spasm of laryngeal musculature; (4) obstructed airway due to abductor paralysis of the vocal cords; (5) accumulation of secretions

due to inability to cough; (6) aspiration of vomitus.

The appearance of laryngeal stridor, dyspnea (despite adequate chest excursion), cyanosis and severe encephalitic symptoms indicates that the obstruction to the airway has not been remedied and that severe hypoxia has now developed. Such symptoms warrant emergency measures to clear the airway. It must be remembered that in patients with partial or complete obstruction of the airway there are strong inspiratory efforts in an attempt to overcome hypoxia. These inspiratory efforts in the face of an obstruction produce a relatively high negative pressure in the bronchioles and alveoli. This negative pressure sucks fluid, plasma and even red cells out of the pulmonary capillaries into the alveoli, producing acute pulmonary edema and death.

If the airway cannot be maintained unobstructed by postural drainage and/or suction, one may have to resort to tracheotomy in selected cases. After tracheotomy patients with bulbar poliomyelitis still require constant care and supervision. It is necessary to continue to aspirate the accumulation of fluids in the pharynx, particularly during the first few days following the tracheotomy. The tracheal cannula must be inspected and cleared frequently. Generally, the tracheal secretions become very viscid and unless the inspired air is adequately humidified, they are very difficult to remove. In order to humidify the inspired air and at the same time deliver a measured amount of moistened air and oxygen mixture directly through the tracheotomy tube, an apparatus called the tracheotomy inhalator has been used by us.[1] This inhalator is so constructed that expiratory and inspiratory pressure can be controlled independently as the emergency demands. This inhalator has the added advantage of permitting the delivery of oxygen mixtures of various percentage concentrations under optimal pounds of pressure. Patients are generally given about 50 per cent oxygen concentration in the inhalation mixture. In all cases oximetry should be employed in order to determine the effectiveness of oxygen therapy. The oximeter is an instrument which determines the relative concentration of oxyhemoglobin to reduced hemoglobin by means of a photo-electric cell. This instrument is of great aid in establishing the efficiency of measures taken to promote adequate oxygenation of the patient in the presence of hypoxia or impending hypoxia.

In spite of tracheotomy and apparent adequate drainage, it has been found advisable to rotate the patient constantly in order to avoid pulmonary hypostasis. This procedure proves most satisfactory providing the patient is rotated at least 30 degrees or more every hour. If the patient is not in a respirator, the rotation should be more complete, extending to the maximum of 90 degrees. Such a procedure has enabled us to keep the lungs clear in many patients in whom pulmonary edema was already developing and has greatly reduced the incidence of our pulmonary complications.

In 100 patients with bulbar symptoms limited to the cranial nerves there were five deaths, four of which occurred before an adequate airway could be secured.

GROUP II: RESPIRATORY CENTER INVOLVEMENT

Many individuals with bulbar poliomyelitis have symptoms and findings indicating involvement of the respiratory center in the medulla in addition to varying degrees of pareses of the cranial nerves. Pathologically, they show in the medulla at the level of the inferior olive, a most extensive bilateral focal necrosis involving the lateral ventral reticular substance. In most cases these lesions consist of areas of inflammatory necrosis, with a fragmentation of the underlying tissues. These inflammatory areas could well be produced by the virus of poliomyelitis. On the other hand, certain of the necrotic areas are filled with fat granule cells and show no evidence of an actual inflammatory process. It is suspected that the etiology of these

latter lesions may well be due to a secondary hypoxia resulting from the respiratory difficulties. Generally the cranial nerve nuclei in the involved areas reveal only minimal changes. Even the nucleus ambiguus, which is situated adjacent to these areas of inflammatory necrosis, is surprisingly free of alterations.

Clinically, the outstanding symptoms are respiratory and correlate with the involvement of the respiratory center in the medulla. During the course of illness irregularities of rhythm and depth of respiration develop. These respiratory symptoms appear in the face of an adequate airway and intact respiratory musculature. The respirations tend to be shallow and there are often prolonged intervals between inspirations. At this point the patients generally show some degree of anxiety, restlessness, increase in pulse rate and some elevation of blood pressure. These symptoms indicate an early hypoxia even though there may be no clinical cyanosis. Such impending failure of the central respiratory mechanism makes it imperative that oxygen therapy be instituted. If oxygen therapy has already been started it is advisable to increase the concentration of oxygen being administered. The effectiveness of the oxygenation can generally be followed by the use of the oximeter and checked by determinations of the arterial oxygen.

As failure of the respiratory center in the medulla progresses, there are increasing periods of apnea with beginning Cheyne-Stokes respiration. The temperature and pulse rate tend upward and the blood pressure may be elevated or may fall to shock levels. Confusion, delirium and coma soon appear. The periods of apnea become more prolonged until finally respirations cease. These latter symptoms require immediate intensification of oxygen therapy; however, the concentration of oxygen used should ordinarily not exceed 60 per cent. In emergencies it may be increased to 100 per cent for a limited period of time. Sedation of any sort should be avoided in this group of patients or should be used with extreme caution because of the depressant effect on an already damaged respiratory center.

GROUP III: VASOMOTOR INVOLVEMENT

A few patients will show severe circulatory collapse with minimal or no cranial nerve palsy and no respiratory involvement. In such cases one is often forced to make a diagnosis of bulbar poliomyelitis in spite of apparently normal function of the cranial nerves. It is this type of involvement that may frequently be overlooked and the diagnosis not made. When the symptoms of bulbar poliomyelitis indicate circulatory involvement, the prognosis generally is extremely grave. The clinical features in this type of bulbar poliomyelitis are very characteristic. These patients have a dusky red, flushed, florid appearance. The lips are deep cherry red. The pulse is extremely rapid, ranging between 150 and 200. It is often irregular and at times difficult to palpate. The blood pressure varies from elevated to low levels, and the pulse pressure may be as low as 10 mm. of mercury. In children the blood pressure has a greater tendency to become elevated. Very early in the illness these patients show marked restlessness, apprehension and anxiety, indicating early onset of a mild or moderately advanced hypoxia. The course in this illness is very rapidly downhill; the skin soon becomes cold, clammy and has a mottled cyanosis. The temperature begins to rise and at the same time the respirations tend to become shallow. Terminally, these patients become markedly confused, finally comatose and the heart beat is inaudible before respirations cease.

At necropsy the lungs seem to be the site of severe hemorrhagic pulmonary edema. Sections through the medulla reveal areas of bilateral focal necrosis which are situated in the medial ventral reticular substance. In most cases one can detect mild inflammatory lesions in the medulla and many of the cranial nerve nuclei show a scattered involvement. These histologic lesions seem very significant in view of the experimental

work of Wang and Ranson[2] who were able to stimulate the brainstem and study the effect upon blood pressure in cats by using the Horsley-Clarke stereotactic instrument. It was apparent from their work that there was a pressor response when the dorsal reticular substance of the medulla just beneath the floor of the fourth ventricle was stimulated. Depressor responses were more diffuse and seemed to be localized primarily in the ventral medial reticular substance of the medulla oblongata. It is in this latter region that we observed pathologic lesions in cases of bulbar poliomyelitis manifesting circulatory symptoms. It would appear, therefore, that when the inflammatory process in poliomyelitis involves the medial ventral reticular substance of the medulla it destroys the vasomotor center and produces marked circulatory responses.

The treatment of the circulatory type of bulbar poliomyelitis is very unsatisfactory at the present time. These patients tend to develop a very rapid pulmonary edema, very severe hypoxia and terminate fatally in a few days. The mortality rate in our cases was 83 per cent. It is believed at the present time that the best treatment consists of intensive oxygen therapy and maintenance of a clear, unobstructed airway at all times. Such oxygen therapy is used to combat the hypoxia and thus prevent the addition of hypoxic damage to centers already injured by the virus invasion. Supportive measures in combating the shock may be used but these seem to be of only temporary benefit.

GROUP IV: SPINOBULBAR INVOLVEMENT

In this group are included those cases in which there is combined involvement of both the medulla and the cervical and thoracic cord. These patients, therefore, in addition to the bulbar symptoms require treatment in the respirator because of the severe damage to the upper part of the spinal cord, resulting in failure of the diaphragm and the intercostal muscles. This combined involvement is discussed in a separate group because it results in specific therapeutic problems which are not encountered in isolated involvement of either the spinal cord or the medulla. The symptomatology in these patients, in addition to the paralysis of the diaphragm and intercostal muscles, will depend upon the region of the medulla involved and will manifest itself either in cranial nerve palsies or as cardiorespiratory disturbances. Because of the involvement of the diaphragm and intercostal muscles it becomes necessary to place these individuals in the respirator. Whenever a patient with bulbar poliomyelitis is placed in a respirator, it becomes imperative to insure an open airway. It must be kept in mind that inspiration forced by the respirator against a partially obstructed airway will create a relatively marked negative pressure in the alveoli, sucking fluid out of the pulmonary capillaries and producing a very acute pulmonary edema. These patients, therefore, must be watched constantly over the twenty-four-hour period to be sure that obstruction does not result. They should be suctioned constantly; and if it appears that the airway cannot be kept open by suction and/or postural drainage, tracheotomy must be considered. In order to use tracheotomy in respirator patients it is necessary to have available a respirator with the front modified so that the respirator head is tilted forward about 6 inches allowing for accessibility to the patient's neck as far as the sternal notch. This modified form of respirator head is now available and can be obtained for the standard makes of respirator. The oximeter is of great value in these patients for indicating the efficiency of the therapeutic measures and determining how long a patient can be left out of the respirator. The appearance of restlessness, apprehension, anxiety, increasing pulse rate and fever indicates an incipient hypoxia, even in the absence of cyanosis, and should alert one to check the patient carefully for possible obstruction to the airway.

In all cases of bulbar poliomyelitis the use of drugs generally is largely prophylactic

and supportive. Since there is a high percentage of pulmonary complications in this disease, intramuscular injections of penicillin are often useful as a prophylactic. In addition, penicillin may be nebulized into the tracheotomy tube at regular intervals if tracheotomy has been performed. When mild anemia develops during the course of the illness, a transfusion of whole blood or plasma is often indicated. Excessive intravenous administration of fluids should be avoided whenever possible, primarily because of the danger of pulmonary edema. Sedatives of any sort should be avoided because of the danger of further impairing bulbar function in an area which is already functioning at a very poor level.

In most cases of bulbar poliomyelitis nutrition is of the utmost importance. During the first few days, particularly if the patient is unable to swallow, it is advisable to use fluids parenterally. Giving any fluids or food by mouth in a patient who is having difficulty in swallowing is extremely dangerous because of the possibility of regurgitation and obstruction of the airway. After the acute stage of the illness has subsided the patient may be fed by nasal tube. In such cases the feedings should be given in very small amounts and sufficient time allowed for absorption. One must always be on the alert for the possibility of regurgitation of such nasal feedings with aspiration of the formula. Not infrequently in bulbar poliomyelitis, the patient develops a complete parasympathetic involvement of the gastrointestinal tract. They have an extremely atonic stomach which will not propel the food into the intestinal tract. This allows the food to accumulate in the stomach and encourages regurgitation and secondary aspiration. Such patients must always be fed very small amounts. This condition can also be improved by the daily injections of prostigmine, 0.5 mg. every two hours. The ability of these patients to swallow should be tested from time to time, beginning with fluids and progressing to soft, and then finally to solid food. When swallowing is fairly well established, the nasal tube can be removed; and if tracheotomy has been instituted, the tracheotomy tube can be stoppered and later removed.

CONCLUSIONS AND SUMMARY

1. Bulbar poliomyelitis, both clinically and pathologically, is not a single entity but can be divided into different groups, depending upon the region of the medulla involved by the pathologic process and the subsequent symptomatology.

2. By far the most frequent type of involvement is that of the cranial nerve nuclei. When the tenth cranial nerve is implicated, difficulty in swallowing and talking develops, with subsequent obstruction of the airway and asphyxia. These symptoms can be prevented by constantly keeping the airway open by means of suction, postural drainage and, when absolutely necessary, tracheotomy.

3. Some cases of bulbar poliomyelitis may implicate the autonomic centers of the medulla; namely, the respiratory and the circulatory centers. In these cases the symptomatology consists of either respiratory or circulatory failure even in the absence of severe cranial nerve involvement. The prognosis in such cases is somewhat doubtful since involvement of the autonomic centers results in very rapid development of hypoxia. The treatment of choice at the present time is intensification of oxygen therapy either by mask, internasal oxygen or by tracheotomy, when indicated.

4. When both the upper spinal cord and bulb are involved, the patient generally must be placed in a respirator. In such cases one must be constantly alert to maintain an open airway in order to prevent rapid pulmonary edema due to the forced inspiration resulting from the use of the respirator.

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Care of the After Effects of Poliomyelitis*

ROBERT L. BENNETT, M.D.
Warm Springs, Georgia

THE obvious purpose of the treatment of the after effects of acute anterior poliomyelitis is to assist the patient to develop the highest possible degree of functional capacity within the unalterable limits defined by the lesion in the central nervous system. Less obvious may be the realization that to achieve this goal our program of care must be based on the philosophy that the end result will depend not only on the damage to the central nervous system but on what is done with what is left anatomically intact and thus potentially available for use. Least obvious is the understanding that the most detailed and exact treatment will fall far short of achieving maximum functional results if all of the factors that determine these end results are not fully understood.

There are four basic factors that determine the end result:

1. *The Site and Extent of Central Nervous System Damage.* This factor is of importance not only because it limits the number of neuromuscular units available for use but also because certain deformities of the skeletal system must follow certain patterns of damage in the nervous system. For example, if a large portion of the nerves that innervate the skeletal muscles of a bodily segment, such as the leg and foot, are destroyed, normal strength and endurance of those muscles can never be obtained regardless of treatment. In a child serious alteration of osseous structure and growth may also occur despite the best of care.

2. *The General Medical Condition of the Patient during the First Few Months after the Acute Illness.* Many patients are so severely involved that their general medical condition prohibits application of convalescent routines that under more favorable circumstances would limit the development of musculoskeletal deformities and faulty patterns of motion. For example, the patient who must be kept in a respirator cannot be cared for adequately and will develop changes in bone, muscle, fascia, joint and peri-articular structures that will be, in great part, irreversible regardless of the highest type of available treatment.

3. *The Caliber of Available Care.* The average patient with residual weakness following poliomyelitis is at best a difficult problem in rehabilitation, requiring for optimal end results the combined skills and experiences of the internist or pediatrician, the physiatrist and the orthopedist. Many patients with only minimal involvement who could be expected to recover normal functional capacity with intelligent care develop severe handicaps because of early weight bearing, unrestricted activity and failure of the attending physician to recognize mild muscle imbalance and incipient deformity. It must be stressed that the patient, child or adult, regardless of how mild the residual involvement may seem, must be repeatedly checked to determine the effect of increasing growth, weight and activity on skeletal structures. The tragedies of progressive deformity, such as scoliosis, can be minimized only if responsible periodic examinations of the musculoskeletal system are made for many years after the acute episode.

4. *The Responsibility and Intelligence of the Patient and/or His Parents.* This factor could be included in the third category but it is of such importance that it deserves special attention. For all practical purposes the general personality of the patient and his

* From the Georgia Warm Springs Foundation, Warm Springs, Ga.

parents is second only to the skill of the physician in assuring the maximum recovery of functional capacity within the limits set by the pathology of the acute disease. It is, of course, impossible to provide hospital bed space for all patients throughout the entire period of their convalescence, but even if it were it would be inadvisable to do so. Prolonged hospitalization is to be avoided because of the danger of mental stagnation and loss of initiative and self-confidence. Return to normal environment and contact with physically normal people are all-important in the overall rehabilitation program. Under ideal conditions the patient should be hospitalized only until the period of rapid recovery has taken place and the correct patterns of movement consistent with the underlying disease have been established. From then on the long-term program to increase strength and endurance by graduated activity can best be carried out at home. In some instances only modified activity is necessary but in most a very definite routine of joint mobilization and graduated exercises must be carried out for many months or even years.

While a program of care must be based on a thorough understanding of the aforementioned factors that determine the possibilities of recovery, the success of the program will depend on the ability of the medical team to achieve four objectives: (1) Effective utilization of all intact neuromuscular units. (2) Prevention or minimizing of all musculoskeletal deformities that would limit the most effective use of these units. (3) Training of patient and parents in their responsibilities within the program. (4) Intelligent acceptance by the patient and his family of his ultimate physical limitations.

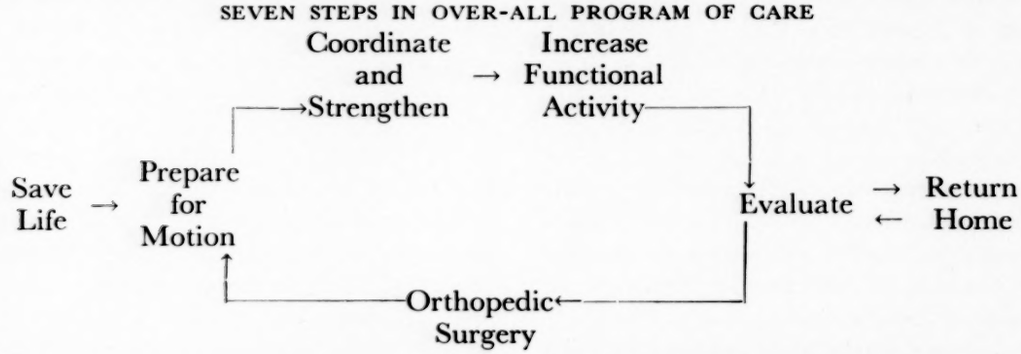
More specifically, a program to achieve these objectives must progress through seven distinct steps that may be outlined in the manner illustrated in the accompanying diagram.

The first step may at first thought be considered unnecessary in a convalescent program but is included to emphasize that certain convalescent routines may actually endanger the patient's life if initiated too early in the acute or subacute phase or at any phase if carried out without regard for the patient's general medical condition.

The second step in our treatment program is the attempt to prepare the patient for resumption of activity. In a great majority of cases this will mean, first, preparation for long and tedious weeks of muscle re-education. It is at this point that a program of convalescent care really begins. The three major points in the preparation of any patient for resumption of activity are: (1) relief of pain; (2) release of any tightness in the muscles and joints; (3) support any bodily segment that is weakened.

It should readily be appreciated that coördinated action of muscle groups acting on any bodily segment is impossible if motion of that segment is limited by pain or by limitation of joint motion. Until this is done we can never fully regain the maximum use of existing myoneural units in any bodily segment. Relief of pain and the release of tightness are accomplished by time plus the use of intelligently prescribed sedatives, heat and passive motion. As in the use of all therapeutic agents the type and frequency of application of heat and motion depend on the reaction of the patient. There is no magical formula to achieve this end by any phase of physical medicine except through the intelligence and responsibility of the attending medical personnel. It is equally important in this step that we begin our endeavor to prevent musculoskeletal deformities. Deformities, except for atrophy and weakness following actual denervation, have just one cause: persistent faulty alinement of bodily segments which results in distortion of bones and joints and fibrous contractures of muscular and ligamentous tissue. In this early convalescent stage of poliomyelitis such malalinement results from persistent faulty posture in bed caused by such factors as pain, muscle weakness, faulty beds or the weight of bed clothes on weakened ex-

tremities. Therefore, it is of importance not only to preserve normal bodily mechanics and alinement by the early restoration of mobility in muscle and joint as just mentioned but also to prevent this persistent faulty posture by the most effective method



possible. An effective support is not only one which holds the segments in proper position but also one which in no way interferes with the other components of early care. It should be quite evident that the type of support will depend on the quality of available medical supervision. Assuming adequate medical supervision is not available, a bivalved plaster cast may be more effective than pillows or sand bags. Under intelligent supervision an orthopedic bed, foot board, properly placed pillows and possibly a light plastic wrist and thumb splint are all the actual equipment needed to prevent deformities at this time.

The third step is to coördinate and strengthen the existing neuromuscular units. Certainly this step is the most important and probably the most difficult one in the entire program. It is in this step that we have made our greatest strides in the treatment of poliomyelitis during the past ten years—not because any outstanding discoveries have been made in functional anatomy or bodily mechanics but primarily because physical medicine has been given an opportunity to use its skill on bodily segments properly prepared for muscle re-education. It is obvious that the success of this step is absolutely dependent on the thoroughness with which the painless and complete mobility of the segment has been restored. It is a continued source of amazement and gratification to see the extent of functional capacity that can be developed by patients with very little muscle power but highly developed coördination. It must be stressed that coördination and power are not the same. Power without coördination may be disastrous to the patient recovering from poliomyelitis because experience has taught us that all muscles in the involved segments do not recover with the same speed. If, as each of these individual muscles come under voluntary control, no attempt is made to coördinate their use, faulty habit patterns of motion will be built up by the patient with the use of these stronger and more easily available groups to the total exclusion of the weaker and thus less available groups. The development of a truly high degree of coördination in the patient with moderate to severe involvement demands the attention of a highly skilled physical therapist. No athlete ever needed a coach as badly as these patients need a physical therapist.

It is of the greatest importance to recognize that during this phase of our program all of our routines are based on the hope that sufficient return of muscular strength will occur to permit normal activity in a perfectly normal manner. It is for this reason that normal patterns of movement are stressed until adequate treatment given over a reasonable length of time has revealed the extent of damage to the nervous system and the limits of recovery possible.

How long should we persist in our en-

deavor to build up the strength of individual muscles by this intensive muscle re-education? The answer can best be summarized in Figure 1.

Experience has taught us that the recovery of strength in individual muscles or muscle groups follows a fairly definite curve or pattern. The end of the third month following the acute onset of weakness, a muscle receiving adequate and intelligent treatment has recovered approximately 60 per cent of the total strength that it will ever recover if treated for an indefinite period of time. During the second three months an additional 20 per cent returns for a total of 80 per cent return at the end of the first six months of adequate treatment. After this the recovery rate becomes increasingly slower so that by the end of eighteen months of treatment it can be reasonably assured that no further increase in individual muscle strength can be expected. By applying this recovery rate curve to specific cases it will be seen that a muscle rating of "poor minus" (10 per cent of normal) at the end of a six-month period of treatment can be expected to gain only an additional 20 per cent of that rating or a total of 12 per cent strength even if treated for a year longer. Obviously 12 per cent of normal strength would mean little or nothing in actual functional value and there would be no justification in treating such a muscle beyond the initial six months time. On the other hand, if a muscle rated "fair plus," or 60 per cent of normal, at the end of the first six months, the possibility of ultimately gaining an additional 20 per cent of that rating (72 per cent of normal) would be well worth working for, particularly if this muscle was one of the important weight-bearing groups.

During this phase the single muscle or muscle group is the unit of treatment. Obviously an accurate grading of these units in the involved segments is essential to the success of muscle re-education. No muscle test is adequate unless individual muscles and not movements are tested. At the Georgia Warm Springs Foundation detailed test sheets are employed to record the strength of these individual muscles. Test sheets that mix muscles and movements brought about by many muscles are to be condemned.

Apparatus may be necessary to assist the

FIG. 1. The usual rate of recovery of individual muscle or muscle group strength under an adequate program of care. Abscissa, time in months; ordinate, per cent recovery.

normal actions of muscles at this time and should be considered a part of the treatment not an admission of defeat. They are applied to allow a more complete return of strength in the full hope that as strength returns they may be discarded.

The fourth step is increasing the actual functional activity of the patient. By the time this step is reached we should be able to determine with a fair degree of accuracy the extent of further improvement that is possible in the individual patient. Certainly, it will be known by then whether a patient will be able to return to a normal environment and carry on normal activities with normal patterns of motion. It will also be fairly obvious at this time whether it will be necessary to add some type of supportive or assistive apparatus to maintain this activity when the patient returns home. It is during this step that specific functional tests are given the patients to determine their ability to carry out certain activities that are required of them in a normal environment. When existing muscle strength and coördination permits, all of these activities are carried out in a normal man-

MUSCLE TEST SHEET, GEORGIA WARM SPRINGS FOUNDATION

No. * Name Date of Birth Age Diagnosis Date of Onset

Cannot Walk	Walks Unaided	With Braces	Left	Right	Crutches	Canes	Corset	Weight
Date								
Date								
Date								
Date								

Characteristic Gait

Date		
Date		

Left	Trunk and Legs	Right
	S.C.M.	
Anterior	Neck	Anterior
Lateral	"	Lateral
Posterior	"	Posterior
	Respiration	
Upper	Back	Upper
Middle	"	Middle
Lower	"	Lower
	Quadratus lumborum	
Upper	Anterior abdominals	Upper
Middle	"	Middle
Lower	"	Lower
Ex. oblique		Ex. oblique
Internal oblique		Internal oblique
	Transversalis	
	Gluteus maximus	
	Ilio psoas	
	Sartorius	
	Tensor fasciae latae	
	Hip abductors	
	Hip adductors	
	Inward rotators	
	Outward rotators	
	Quadriceps	
Inner	Hamstrings	Inner
Outer	"	Outer
	Gastrocnemius	
	Anterior tibial	
	Posterior tibial	
	Peroneals	
	Extensor longus digitorum	
	Extensor brevis digitorum	
	Extensor proprius hallucis	
	Flexor longus digitorum	
	Flexor brevis digitorum	
	Flexor lumbricales	
	Flexor longus hallucis	
	Flexor brevis hallucis	
	Measurements	
Inspiration	Chest	Inspiration
Expiration	"	Expiration
	Calf	
	Thigh	
	Length	
	Contractures and Deformities	
	Hip	
	Knee	
	Ankle	
	Scoliosis	
Anterior	Deltoid	Anterior
Middle	"	Middle
Posterior	"	Posterior
Upper	Trapezius	Upper

Left	Trunk and Legs	Right
Middle	"	Middle
Lower	"	Lower
	Serratus magnus	
	Rhomboids	
	Latissimus dorsi	
Clavicular	Pectoralis major	Clavicular
Sternal	" "	Sternal
	Outward rotators	
	Inward rotators	
	Biceps	
	Brachioradialis	
	Triceps	
	Supinator brevis	
	Pronators	
Ulnar	Wrist flexors	Ulnar
Palmaris longus	" "	Palmaris longus
Radial	" "	Radial
Ulnar	Wrist extensors	Ulnar
Radial	" "	Radial
1 Profundus	Finger flexors	Profundus 1
2	" "	2
3	" "	3
4	" "	4
1 Sublimis	" "	Sublimis 1
2	" "	2
3	" "	3
4	" "	4
1	Finger extensors	1
2	" "	2
3	" "	3
4	" "	4
1	Lumbricales	1
2	"	2
3	"	3
4	"	4
1	Dorsal interossei	1
2	" "	2
3	" "	3
4	" "	4
	Abductor minimi digiti	
1	Palmar interossei	1
2	" "	2
3	" "	3
	Abductor longus pollicis	
	Abductor brevis pollicis	
	Adductor pollicis	
	Flexor longus pollicis	
	Flexor brevis pollicis	
	Opponens pollicis	
	Extensor longus pollicis	
	Extensor brevis pollicis	
	Contractures and Deformities	
	Shoulder	
	Elbow	
	Wrist	
	Fingers	

ner. If it is obvious that the damage to the motor system of the central nervous system is such that normal patterns of motion can never be achieved, the patient is given the necessary apparatus to support the activity and taught the most effective ways of using this apparatus. If necessary, specially designed assistive types of apparatus are made for the individual patient. It might be perfectly possible for one patient to achieve normal activity without any type of brace, crutch or corset whatsoever. Another patient might be able to achieve the same activity but only by using a long leg walking brace. Another patient, however, might have such severe involvement that walking will never be safe or practical, and that actually teaching him to care for his own personal needs through the use of specially made splints or feeders will be his maximum functional capacity.

The fifth step is the attempt to evaluate

FUNCTIONAL TEST SHEET
Georgia Warm Springs Foundation
Functional Evaluation

Name:_____ Age:_____ Onset:_____
Occupation:_____ No._____
Apparatus:_____

Grades Indicating Independence
- N Normal performance—patient apparently uninvolved.
- G+ Excellent performance—involvement apparent but speed, safety, endurance, and agility in performance no problem.
- G Adequate performance for all practical purposes.
- G— Adequate performance in a specific environment—limited to special types, styles, weights, heights, etc.

Grades Below Independence
- F Performance possible but not practical (speed, safety, etc.).
- P Performance is partial only (Example: Can get into chair but not out of it.)
- ? At this stage of treatment patient not allowed to perform the activity.
- X Activity not indicated for testing.
- O Activity impossible.

9 Bed (%)
Operate signal light
Hold letter
Hold book
Turn pages
Write name
Operate bed lamp and radio
Procure object from night table
Sit up
Turn over

6 Eating (%)
Eat with fingers
Eat with fork
Eat with spoon
Drink from glass
Drink from cup
Cut with knife and fork

13 Hygiene (%)
Use handkerchief
Wash hands
Wash face
Brush teeth
Comb hair
Clean nails
Trim nails
Shave or make up
Get on and off toilet
Use toilet paper
Bathe self
Get in and out of bath or shower
Shampoo hair

7 Dressing (%)
Put on—remove underclothes
Put on—remove buttoned shirt
Put on—remove slipover garment
Put on—remove slacks
Put on—remove shoes
Put on—remove hose
Tie bow or tie

5 Apparatus (%)
Lock and unlock braces
Put on—remove slings
Put on—remove splints
Put on—remove corset
Put on—remove braces

16 Utilities (%)
Operate door bell
Operate flip light

Small letter beside grade or symbol indicates:
- w Possible in wheel chair (Example: G w)
- b Possible in bed (Example: G b)
- No letter = Possible standing (Example: G)

Grade with circle = Assistive, supportive or mechanical apparatus necessary for that grade (Example: (Ⓖ)) (Example: G✓)

✓ Working on improving performance of activity

Percentage of Independence in Each Section
Count number of grades indicated for testing.
Count number of independent grades.
Divide number of independent grades by the number of grades indicated for testing to obtain the percentage of independence in each section or use percentage chart.

Operate pull light
Operate faucet
Operate hook and eye latch
Operate hasp and padlock
Operate barrel bolt
Operate inside door set
Operate night latch
Operate venetian blind
Plug in cord
Wind watch or clock
Open and close drawers
Open and close windows
Use needle and thread
Use scissors

6 Communication (%)
Write or type test passage
Handle own mail
Handle money
Use dial 'phone
Use pay 'phone
Wrap and unwrap package

24 Locomotion (%)
Roll wheelchair on smooth surfaces
Roll wheelchair on rough surfaces
Control wheelchair down grade
Roll wheelchair upgrade
Open common doors, go through, and close
Operate automatic elevator
Move on floor not in upright position
Walk on smooth surfaces 100 yds
Walk through an aisle of seats
Walk on rough surfaces
Walk up and down 20 degree grade
Walk forward and backward carrying object
Cross street with traffic light
Get in and out of wheelchair
Get in and out of chairs
Get in and out of bed
Get in and out of car
Do 7 inch rise steps with rails
Do 7 inch rise steps without rails
Do plane steps
Do bus and train steps
Pick up object from floor
Get down and up from floor
Drive car

Specialties

a patient, not only in terms of what he can do at the present but whether further treatment is necessary to increase his functional capacity and to assure his future security.

All patients regardless of involvement should be completely evaluated by the physiatrist and orthopedist before dismissal from the hospital. On the basis of this evaluation the present status and probable ultimate involvement should be thoroughly discussed with the patient and/or his family. Instructions in all necessary treatment to be continued at home can be given at this time as well as definite instructions in type and extent of activity and the time of the next medical check-up.

The sixth step is usually the return to a normal environment. Before this step is actually made both the patient and his parents should be fully acquainted with the patient's entire problem and the possibility of any change in his status in the future. In a great majority of patients treatment at home must be continued for many months, interspersed with repeated medical examinations to determine the need for additional treatment, either as a means of increasing the patient's functional capacity or perhaps minimizing certain deformities that seem to be occurring.

Thus a patient from the sixth block of a normal environment might return to the fifth block of evaluation and then be sent back into the treatment program, either for increased coördination and strength of muscle effort or for some phase of increased functional activity; or perhaps at this time he will be referred directly to the orthopedist for certain orthopedic procedures.

No medical program for the care of the after effects of poliomyelitis is complete unless it provides for adequate follow-up of its patients. Maximum return of strength, endurance and functional activity may require years of guided effort. Many deformities will not occur nor existing deformities progress until many years after the onset of the disease. Likewise, many supportive, corrective and assistive orthopedic procedures cannot be carried out with optimum results until patients reach a period of solid bone formation. The doctor must maintain contact with his patient until maximum functional capacity has been obtained and future security established.

The seventh step is that of orthopedic surgery at which time the surgeon endeavors to determine whether certain procedures can increase the patient's ability to function with either greater effectiveness or endurance, but more particularly to determine whether the patient's increasing growth, height, weight and activity can be supported on weakened segments without damage to them. In a great many instances, before any consideration can be given to increased functional capacity and security, the orthopedic surgeon must correct deformities that have occurred during the convalescent period.

The continued physical security of the patient is the most serious responsibility of orthopedic surgery. It is absolutely necessary to foresee the effect of growth, increasing weight, age and activity on weakened bodily segments and to take adequate precautionary measures when relatively simple surgical procedures will prevent the occurrence of irreversible structural changes. Ideally, surgery should be considered not as a last resort after the damage is done but rather as a means of preventing these tragedies. It is obvious that the results obtained by the orthopedic surgeon depend on the thoroughness of the conservative care during the period of convalescence. Certainly, if fairly normal skeletal alinement and joint mobility have been preserved, the surgeon can do his work more efficiently.

It is essential that we foresee the possibility of later surgical procedures throughout all early phases of convalescence. It is equally important to point out that certain surgical procedures are needed during the convalescent stage. In general, it has been stated that when orthopedic surgery is indicated to correct a deformity, increase

functional capacity and assure future security of bodily segments, it should be deferred until the chronic stage or, in children, after bone formation is well advanced. This is only partially true. Relatively simple surgical procedures, such as sectioning of the iliotibial band or heel cord if done early in a convalescent program, often permit restoration of bodily alinement possible in no other way. This not only prevents irreversible and severely handicapping changes from taking place but also permits more effective use of muscle re-education and functional training.

SUMMARY

To achieve restoration of maximum functional capacity possible within the limits imposed by the actual damage to the nervous system requires a logical sequence of treatment steps. Chronologically, this treatment program is well defined by the recovery rate expectancy curve and the age of the patient.

Public Health Considerations of Poliomyelitis*

JOSEPH G. MOLNER, M.D.
Detroit, Michigan

THE health officer is expected to control public health problems and it is his responsibility to the citizens of the community which he serves to do so, or at least to employ the best available knowledge and methods for the protection of the public health. When an epidemic of disease occurs, be it an epidemic of measles, of smallpox, of typhoid fever, or of poliomyelitis, an epidemic of a disease for which effective control measures are available or a disease for which there are no known control measures, the citizens naturally turn to him.

The methods for control, or rather attempted control, of those diseases which may occur in epidemic proportions and those diseases which are communicable have undergone many radical changes in recent years. Many restrictions, for example quarantine, were used not on the basis of scientific evidence but primarily because the ways and means by which diseases were spread were not known; often the utilization of quarantine was a grasp at the proverbial last straw. Despite the general tendency among public health workers of the present day to discredit and discontinue quarantine as a method of control during an epidemic of disease the community often demands the institution of this procedure. Here is a method which is familiar, which had been used for many years with apparent official approval and the health officer through the force of public opinion and to allay anxiety is virtually forced into the adoption of an only potentially valuable control measure of limited practical applicability.

In spite of pressure groups of any type it is one of the first and most important functions of the health officer to weigh preventive procedures on the basis of available scientific facts. He is in a difficult position, however, because frequently much publicized information emanates from the scientific laboratory, from the desk of the epidemiologist or the office of the clinician and the information may be related only remotely to the prevention of disease. The public is apt to accept such information without question as a panacea and the health officer is expected to apply the panacea within his jurisdiction. Admittedly, the health officer has in addition to the responsibility for weighing the potential need of preventive measures, the responsibility for the field evaluation of such measures. However, before embarking upon their adoption, even on an experimental basis, these procedures must be weighed carefully and studied for their probable value as preventive measures, relative ease of enforcement and economic effect upon the individual, the household and the community. If such measures are found to be administratively sound and financially practical, they should be put into effect as the policy of the organization, as an epidemiologic supplement or as administrative research.

Just what should the health officer do when poliomyelitis strikes?

EDUCATION

Certainly one cannot help but believe that of the many dangerous diseases poliomyelitis appears to have the most adverse psychologic effect on the public, and it is the responsibility of the health officer not only to alert the public, including

* From The Detroit Department of Health, Detroit, Mich.

physicians, to the increased incidence of the disease but to gear the health education services of his organization to present authentic information and to prepare and submit it in a manner which will most effectively avoid panic and allay anxiety.

Satisfactory Press Relations. The public press and the radio represent two of the most important outlets for lay information, and a cooperative press releasing facts instead of fancy about poliomyelitis is of inestimable value. The health officer must secure proper contact with the press and prepare information concerning the disease in an intelligent and understandable form. The press is always anxious to carry facts and when misinformation is printed it is because of misunderstanding rather than misrepresentation. We know that a press which dramatizes or exaggerates facts can create anxiety and cause a great deal of damage. It is therefore of paramount importance that the health agency secure the cooperation of the press. This may, of course, be accomplished most satisfactorily by making available to the news gathering agencies properly prepared information in a language which their readers can readily understand.

Alerting the Public. There are many other ways of alerting the public to the significance of an epidemic of disease. To illustrate a few of these we need to mention parent-teacher associations, mothers' clubs, health guild and, of course, the radio and possibly television.

Contrary to the old attitude, there is very little information concerning the communicability, clinical significance, complications and treatment of disease which cannot be made available to the thorough understanding of the public if such material is properly prepared and presented. It is this fuller knowledge of sickness which stimulates greater cooperation.

Informing the Physician. It is with no embarrassment that physicians admit the need for information concerning poliomyelitis. With the relatively low rural epidemic attack rate and even lower urban attack rate, with the relative infrequency of epidemics, it is not very often that a physician is called to see a patient or a suspicious case of poliomyelitis.

It is considered important that the physician be in a position to answer the questions directed at him by his patients, and it is important especially during the time of an epidemic that the information released from the official health agency be coordinated with the information which patients receive from their family doctors; contradictory answers or apparent disagreement between the physician and the health agency tend to create lack of confidence in both. The physician, therefore, must have the facts concerning poliomyelitis at least at the same time, preferably before, the information is given to the public.

The physician's lack of experience with poliomyelitis may lead to an inadequate appreciation of the real significance of the disease. The health officer must therefore confer with local physicians early in an epidemic and discuss the facts related to poliomyelitis as a disease and as an epidemic afflicting the community.

To inform physicians concerning poliomyelitis, or any public health problem, postgraduate conferences are of inestimable value. Conferences of this type should be conducted under the auspices of the local medical society, the health department and any interested unofficial agency. This type of conference has been in existence in many parts of the United States for many years and has been exceptionally well patronized by the medical profession. Speakers generally include members of the local medical society, the local health officer and at times authorities from other sections of the country.

Not all the essential information concerning the medical and public health aspects of poliomyelitis can be presented in conferences of this type nor can it be expected that all physicians will attend. Therefore, published information directed toward the physician either in local official publications or through communications

from the health department should supplement the conferences.

The health services of a community should also be geared to lend consultation to the private practitioner of medicine in the diagnosis and treatment of disease. Diagnostic services, in addition to clinical consultation, should, of course, include laboratory facilities for aid in diagnosis.

The agenda for education of the physician must include the most recent and best information concerning the epidemiology of the disease, for example, probable sources of infection, probable modes of transmission, incubation period, susceptibility and prevalence. There must be included in these discussions the criteria of early diagnosis, the significance of paralytic and non-paralytic disease and the need and significance of laboratory methods for the diagnosis of poliomyelitis. It must be emphasized that during an epidemic all cases of unexplained fever or other symptoms which may be related to poliomyelitis should be regarded with extra care lest they be the signs and symptoms of non-paralytic poliomyelitis.

The clinical classifications of poliomyelitis and the significance and value of the latest and most modern therapeutic regimens should also be presented, with proper emphasis placed upon those proposed and sometimes publicized therapeutic measures which may be of only potential value or of no value. It is important that the physician know of the community facilities which are available for the care of those with acute cases of poliomyelitis as well as the complications of the disease.

From the public health point of view it is appreciated that all cases diagnosed either as suspicious or actual cases should be reported to the health agency. The significance of this reporting must also be called to the attention of the physician.

PREVENTION

No phase of communicable disease control is of greater importance to the public and to the physician than those measures which will prevent or which may modify disease. During an epidemic of poliomyelitis there is more misinformation concerning this public health aspect of the disease than any other. The preventive phases of poliomyelitis must be stressed to the physician and to the public.

The significance of early recognition and isolation of active and suspicious cases and the importance of the carrier state in poliomyelitis, together with the relative ineffectiveness of quarantine measures, should also be given special consideration. It is only proper with our most recent knowledge concerning the discharge of the virus from the human body that human excrements be properly removed from potential intimate contact with the human population. No major changes are necessary in community facilities for the collection or disposal of human excreta but certainly proper and careful disposal of excreta within the isolation area is indicated.

Because flies may play an important role in the transmission of the disease and because the protection of food from flies is an essential public health measure, screening of homes, destruction of flies and protection of food from flies should be recommended.

Since person-to-person contact is probably the most important of the many proposed theories of the mode of transmission of the disease and because circumstantial evidence strongly supports this proposal, it should be recommended that persons, particularly children, do not travel to or from the epidemic area. The closing of community borders, schools and churches is not recommended; by the time such measures are initiated the seeding of infectious agents in the community or in the area would be so extensive that at best they would be only gestures or futile attempts.

However, in the event that poliomyelitis occurs in epidemic proportions at the time that schools are to be opened it may be considered a measure of expediency to delay their opening. It is considered expedient to protect children so far as practi-

cable against unnecessary contact with persons outside their homes, and it is recommended therefore as good practice during an epidemic of poliomyelitis to keep children away from swimming pools, wading pools, theaters and churches. There is reasonably good evidence to indicate that trauma, exertion and fatigue may predispose to poliomyelitis and avoidance of these conditions should also be recommended.

Of the many proposed preventive measures there is probably none more important than deferment of elective tonsillectomies or elective operations of the nose and throat during an epidemic or just preceding expected high incidence or epidemic proportions of poliomyelitis since there is good evidence to show that recent tonsillectomies are predisposing to bulbar poliomyelitis. Emergency tonsillectomies must be left to the discretion of the family physician.

NURSING VISITS

A well co-ordinated program in public health calls for nursing visits to the homes of patients. These are not for the purpose of caring for patients because all poliomyelitis patients should be cared for in hospitals. Public health nursing calls are made primarily to consult with the families of patients and to lend assistance in any way possible. The public health nurse as a family health counsellor in these situations can be of invaluable service.

HOSPITALIZATION

Treatment of infantile paralysis with modern methods is complicated and expensive. Hospital care is essential and hospital facilities for the care of poliomyelitis should be available in every locality. This poses a very important problem for the health administrator because in spite of the generally admitted theories that poliomyelitis is not a highly communicable disease, that the secondary attack rate is virtually negligible and that patients may be cared for in general hospitals, most general hospitals resist admission of poliomyelitis patients for fear of institutional epidemics. There is, therefore, need for education of the hospital administrator as well as the medical staff of the institution to the fact that poliomyelitis can be cared for without unusual risk in general hospitals during the acute as well as during the convalescent stages. Poliomyelitis patients can certainly be cared for in general hospitals without risk to other patients and personnel if the usual precautionary measures used in the care of other types of diseases are invoked. Such care implies isolation precautions, reasonably careful technic in handling of the patient and proper disposal of excreta.

The health department, in cooperation with the medical profession and with other official and non-official agencies, must be the driving force if not the supplier of adequate medical care for poliomyelitis patients. Needless to say, it is preferable that the health department be the driving force in making adequate care available.

This will involve availability of hospital facilities for care of the patient during the acute stages and equipment and materials for administration of the most modern methods of therapy. Under present methods of therapy equipment such as respirators, hot pack machines and physical and occupational therapy equipment for the convalescent care and rehabilitation of patients is required.

Proper care of patients will include well trained personnel conversant with modern therapeutic measures and physical therapists properly trained in administration of newer treatments. It is important to have occupational therapists well versed in the problems of the convalescing poliomyelitis patient and the means by which these patients may be brought back to the ultimate of self-sufficiency and productiveness. This may necessitate special training for the available personnel or the recruitment of new personnel who have been trained in the care of poliomyelitis patients.

The health department has an important responsibility in the promotion of available and good care for poliomyelitis patients regardless of their economic status.

Modern and effective methods for the treatment of poliomyelitis have pyramided the cost of medical care to the point where such service is virtually beyond the reach of the majority of the population. In many states funds are available through official organizations and funds may be made available through non-official agencies, but the important thing is that care, regardless of the source of financing, must be available for the patient.

Many treatment phases of poliomyelitis do not require professional personnel. With the shortage of professional personnel, lay persons can be trained to apply hot packs and to administer the simpler types of physical therapy.

EPIDEMIC COMMITTEE

In keeping with the thought that a well informed community is a cooperative community, it has been found expedient to organize at the time of an epidemic a citizens' committee to assist in the management of the various problems which arise and to assist in the dissemination of information concerning poliomyelitis and the epidemic in existence. A committee of this type, composed of leaders in the community, for example, ministers, teachers, attorneys, bankers and public officials, can do a great deal in disseminating reliable information concerning the epidemic, procurement and even training of personnel and procurement of hospital beds and equipment.

Citizen committees of this type have been organized on several occasions during an epidemic of poliomyelitis and have functioned very successfully. It must be emphasized, however, that these committees must be working committees rather than figureheads—committees in name only can be obstructive.

CONCLUSIONS

The public health considerations of poliomyelitis herein discussed are for the most part non-specific. There are but very few specific preventive measures which can be applied or effectuated as far as the public health aspects of poliomyelitis are concerned. The measures presented, however, are quite generally accepted and represent the best judgment of many public health officials and research workers. Until such time as the epidemiologist, the laboratory worker or the clinician make available to the public health officer more specific means of control, such as active or passive immunization, the public health approach with probable modification will remain much the same as outlined in this paper.

End of Symposium on Poliomyelitis

Clinical Studies

Adrenal Medullary Tumor (Pheochromocytoma)*

FRANCIS N. HATCH, M.D., VICTOR RICHARDS, M.D. *and* RALPH J. SPIEGL, M.D.
San Francisco, California

PHEOCHROMOCYTOMAS are tumors of the chromaffin cells of the adrenal medulla. These cells are derived from the neuroectoderm of the neural crest and are developmentally related to the matured cells of the sympathetic ganglia. Paragangliomas are tumors of the paraganglia, aggregates of chromaffin cells found apart from the adrenal medulla in association with the ganglia of the sympathetic trunk and plexuses and occasionally in relation to viscera where they may have arisen in common with the peripheral sympathetic ganglionic groups; they may also arise from the coccygeal or carotid bodies. Few paragangliomas are true chromaffin-cell tumors, and they rarely produce cardiovascular symptoms. Pheochromocytomas, in contrast, have been aptly described as histologically benign but physiologically malignant; most of them cause either paroxysmal or sustained hypertension.

Adrenal pheochromocytomas are usually encapsulated, small, round and unilateral; however, they may be large (reported up to 12 cm. in diameter and weighing 2,000 Gm.) and bilateral (16 of the 152 cases reported by MacKeith).[1] If malignant, metastases are most frequently found in the regional and thoracic lymph nodes, liver and skeleton. The very large tumors are frequently cystic and hemorrhagic. The granules of the tumor cells give a characteristic brown "chromaffin" reaction when stained with chromium salts. Adrenalin assays of the tumor tissue have varied from 0.12 to 20.0 mg. per Gm.;[2] the normal adrenal medulla contains about 0.4 mg. of epinephrine per Gm.

In 1886 Frankel[3] reported finding bilateral adrenal tumors at the autopsy of an eighteen year old girl. Labbé, Tinel and Doumer[4] wrote the first detailed clinical-pathologic description of the associated paroxysmal hypertension in 1922. A correct clinical diagnosis was reported in 1926,[5] but the first experience in preoperative diagnosis, successful excision and symptom-free survival was not described until 1929.[6] In 1937 increased amounts of epinephrine were demonstrated in the blood of patients during attacks;[7] MacKeith[1] in 1943 reviewed the reports of 152 patients with adrenal pheochromocytoma and nine with paraganglioma associated with the adrenal-sympathetic syndrome. Since his paper appeared, at least twenty-six additional cases have been described. The best reviews of the subject are those of Belt and Powell,[2] Howard and Barker,[8] McKenzie and McEachern[9] and MacKeith.[1]

CLINICAL MANIFESTATIONS

Pheochromocytomas are found equally distributed in both sexes, most commonly during the third to fifth decades and more frequently in the right adrenal. As stated by MacKeith these tumors may cause "(1) Recurrent paroxysms of generalized vasoconstriction accompanied by a remarkable but transient hypertension—*the adrenal-sympathetic syndrome;* (2) chronic hypertension with renal and cardiac failure, resembling malignant hypertension; (3) Addison's disease from local pressure on the cortex, an uncommon picture, or (4) no symptoms." Hirsutism, precocious genital development and other evidences of adrenal cortical

* From The Departments of Medicine and Surgery, Stanford University School of Medicine, San Francisco, Calif.

disturbance have been reported.[10] Those cases of sustained high blood pressure may resemble essential hypertension from the onset. Patients with typical hypertensive crises early in their clinical course may enter a later stage of continuous hypertension. In some, paroxysms are superimposed upon a state of persistent hyperpiesis. The patients with paroxysmal attacks are clinically most common, most readily recognized and therapeutically most hopeful. The history may indicate attacks over as long as sixteen years. The initial attack may be as severe as subsequent episodes, but often the early symptoms are mild and equivocal: transient malaise, headaches, nausea, vague pains or dizziness may recur unexplained until typical crises suggest the diagnosis. Attacks may occur only at long intervals or as often as several times a day.

TABLE I
FREQUENCY OF OCCURRENCE OF PRINCIPAL SYMPTOMS IN EIGHTEEN CASES OF PHEOCHROMOCYTOMA
(Howard and Barker, 1937)

Symptoms	No. of Cases
Blanched, cold extremities	17
Palpitation	17
Nausea	16
Sweating	14
Vomiting	13
Headache	10
Pulmonary edema	9
Precordial pain	8
Dilated pupils	4
Body tremors	3
Dizziness	2

Crises are characterized by sudden, generalized vasoconstriction that produces both local and generalized effects. Table I, listed by Howard and Barker[8] from a review of eighteen cases, is representative of the described symptomatology of reported series. MacKeith[1] described the clinical variations in detail. Some patients experience symptoms limited to only one region, such as episodic abdominal pain and vomiting, or recurrent headaches. Brief antecedent malaise or paresthesias may initiate the attack. Palpitation is usually the first symptom, but vague uneasiness, lassitude, weakness or regional pain in the abdomen, chest or head may provide the subjective warning. Vasoconstrictive effects—cramps, colic, etc. —may begin in the lower part of the body and progress cephalad to cause successive anginal constriction, dizziness and severe headache. During severe episodes the patient is unmistakably ill and the attack may terminate in a state of shock. Blanching and pallor of the face and extremities are common although there may be alternate flushing or no obvious color change of the skin. Tachycardia, bradycardia and irregularities of rhythm may occur. The pulse is usually weak. Accentuation of the aortic second sound and transient aortic diastolic murmurs have been noted. The systolic blood pressure may rise 100 to 200 mm. of mercury above the interim levels, with an associated diastolic increase. During attacks there may be dilatation of the pupils. Hyperglycemia and glycosuria are other effects of increased discharge of epinephrine. In about one-third of the cases a tumor is palpable in the abdomen or flank. Massage of such tumor, or of the loin or abdomen if a palpable mass is not present, may induce an attack. It should be emphasized, however, that failure to cause an attack by this means does not preclude the diagnosis of chromaffin-cell tumor; furthermore, if a mass is not felt, an attack may be induced by massage but this is not to be taken as evidence that the tumor is on the side of the abdomen manipulated. (Table II.)

Attacks may last for a few minutes or persist for hours or days. In at least half the cases crises occur spontaneously, but in many instances one or more precipitating factors have been noted. These include postural changes (most commonly), nervousness, emotional stress, physical exertion, pain, constipation and menses. Clinical complications are dependent upon degree and duration of the induced hypertensive state. Progressive alterations include arteriosclerosis, cardiac hypertrophy, retinal and renal damage; acute effects which account for sudden fatalities are pulmonary edema, cerebral hemorrhage and shock.

Differential Diagnosis. The diagnosis of pheochromocytoma may be obvious in the

observed presence of typical paroxysms with the rise of blood pressure and attendant objective vasomotor manifestations. If a palpable tumor is also present or attacks may be induced, the evidence is conclusive. The absence of clearly defined attacks does not invalidate the diagnosis but forces other considerations. These are grouped in Table III in categories of diagnostic probability.

TABLE II
BLOOD PRESSURE OBSERVATIONS IN EIGHTEEN CASES
(Howard and Barker, 1937)

Case	Age	Sex	Duration of Symptoms	Blood Pressure —Resting	Blood Pressure —In Attack
1	28	F	Several months	150/100	260/180
2	30	F	1½ yr.	130/82	+300/180
3	37	M	1 yr.	140/80–210/130	+300/180
4	29	M	10–11 yr.	160/100	300/?
5	26	F	10 yr.	120/90	260/120
6	39	M	6 mo.	110/?	+200/?
7	46	M	9 yr.	160/120	280/120
8	29	M	1½ yr.	150/115	325/200
9	41	M	1½ yr.	200/100	340/110
10	36	F	5 mo.	125/105	300/240
11	16	M	5 mo.	125/105	300/200
12	45	F	7 yr.	170/80	+300/240
13	40	F	11 yr.	185/105	290/160
14	45	M	7 mo.	140/90	+260/120
15	37	F	7 yr.	100/60–130/90	220/130
16	38	M	17 mo.	225/160	330/120
17	69	M	3 yr.	112/70	260/120
18	27	F	4 yr.	120/80	240/180

TABLE III
DIFFERENTIAL DIAGNOSIS IN CASES OF PHEOCHROMOCYTOMA

Likely
Essential or malignant hypertension
Acute and chronic nephritis
Hyperthyroid state
Cushing's disease
Polyglandular dyscrasia
Brain tumor
Mediastinal tumor

Unlikely
Diabetes mellitus
Angina pectoris
Peptic ulcer
Tabetic crises
Migraine
Epilepsy
Periarteritis nodosa

Confusing
Neurasthenia
Anxiety state
Cardiac neurosis

LABORATORY TESTS

The patient suspected of having a pheochromocytoma is routinely subjected to many laboratory and a few clinical tests. These are briefly tabulated in Table IV. Negative or equivocal results are frequent. The most specific test is the demonstration of increased amounts of epinephrine in the blood during or even between paroxysms.[11] This is cumbersome and the test is not always positive even in the presence of the tumor. The histamine test was first described by Roth and Kvale.[12] This test was based on the assumption that the opposing physiologic effects of histamine and epinephrine might be utilized during the surgical excision of pheochromocytoma to prevent responses to the excessive epinephrine blood levels provoked when the tumor is handled. However, a contrary effect was produced; very small amounts of histamine base given intravenously caused hypertensive crises with the signs and symptoms of paroxysmal sympathetic attacks. This experience has provided a simple clinical test for chromaffin-cell tumors. Histamine base, 0.025 or 0.05 mg., given intravenously will cause a systolic pressure rise of at least 100 mm. of mercury if the tumor is present. Headache and the usual sympathetic symptoms may be severe and the effects last as long as ten minutes in some cases. The test has been positive in 100 per cent of the few cases described to date.[13]

More recently a similar test utilizing the "adrenolytic" action of benzodioxane drugs has been reported. In May, 1947 Snyder and Vick[14] described the use of this diagnostic aid in two children with pheochromocytoma. Goldenberg, Snyder and Aranow subsequently presented a detailed discussion of the drugs and the test, with a report of two additional cases.[15] The structural formulas and pharmacologic relationship between the adrenolytic benzodioxanes and the sympathomimetic phenylethylamine are indicated in their paper. Fourneau and Bovet[16] first investigated the benzodioxanes. Many chemical variants were tested; those selected for clinical trial because of their minimal toxicity are designated 1164F ([2,4,-dimethylpiperidyl]

methylbenzodioxane), 933F (piperidyl-methyl benzodioxane) and 1071F (dimethylaminomethyl benzodioxane).

The basis for use of these drugs is that in non-toxic dosage their action is adrenolytic rather than sympatholytic. Thus in the presence of pheochromocytoma the attendant increase in circulating epinephrine is counteracted and a fall of blood pressure effected; in hypertension from other causes, including "essential hypertension," a minimal effect, no effect or a purely pressor response is produced. Normal subjects respond with a mild pressor effect.

TABLE IV

LABORATORY AND CLINICAL TESTS IN THE DIAGNOSIS OF PHEOCHROMOCYTOMA

1. Epinephrine: increased blood level during or between attacks
2. Histamine: 0.025–0.050 mg. of base intravenously: symptomatic simulation of paroxysm; rise in systolic blood pressure 100 mm. Hg or higher
3. Benzodioxane drugs (Fourneau): "adrenolytic agents," intravenously: rapid fall of systolic and diastolic blood pressure
4. Glucose tolerance test: decreased tolerance, impaired carbohydrate metabolism; frequently normal
5. Basal metabolic rate: to exclude hyperthyroid state; may be greatly elevated by pheochromocytoma[20]
6. 17-ketosteroid excretion: inconsistently affected by adrenal medullary tumor
7. X-ray demonstration of adrenal tumor: excretory or retrograde pyelography which may fail; perirenal air insufflation which is more reliable but hazardous
8. Electrocardiogram:
   abnormalities of rhythm
   conduction defects
   altered T waves
   shifts of axis
   } nothing characteristic

The technic for using these drugs and interpreting the test is detailed by Goldenberg et al.[15] A continuous intravenous drip of normal saline is given to the unsedated patient during the rest period preceding introduction of the drug. The dosage used was 10 mg. of 933F or 30 mg. of 1164F per square meter of body surface given over a two-minute injection period while the intravenous drip continued. The duration of the drug action was usually less than fifteen minutes. Blood pressure readings were taken at frequent intervals before, during and after drug injection, until the pressure returned to the pre-administration levels. Interpretation of results was facilitated by plotting the pressure changes against time. In three patients with pheochromocytoma the maximal reduction of systolic and diastolic pressures was from 50 to 70 mm. of mercury; pre-injection pressure levels were regained in about fifteen minutes.

Side actions of the benzodioxane drugs were not serious. They included sinus tachycardia, flushing, palpitation, nervousness, cold and clammy extremities, hyperpnea, mild headache, fright, sighing respiration and dizziness. This test is therefore preferable to the injection of histamine from the subjective standpoint. The use of neither test has yet produced a seriously untoward response but the reported series for each is small, and the danger of inducing either a marked rise or fall of blood pressure in the hypertensive subject should not be forgotten.

TREATMENT

Pheochromocytomas are treated by surgical excision; there is no medical therapy except ancillary in preoperative and postoperative care and palliative during paroxysms. Morphine or codeine, sedatives, and vasodilator drugs may be helpful in an attack. Phlebotomy and lumbar puncture have been suggested for prolonged episodes. MacKeith states that epinephrine is specific in treating postparoxysmal collapse.

Pre- and postoperative care have been fully discussed by Biskind, Meyer and Beadner[17] in a review of all patients treated surgically to 1940. Because these tumors are frequently accompanied by adrenal cortical deficiency, they recommend a high salt diet with 4 Gm. of additional salt by mouth for two days, 5 mg. of desoxycorticosterone intramuscularly the day before and the day of operation and the injection of 10 cc. of adrenal cortical extract during excision and as needed in the postoperative period. The choice of anesthetic seems to be induction with avertin or tribromethylene followed by ether-nitrous oxide inhalation. Spinal anesthesia is contraindicated. Sharp fluctuations of blood pressure during the operation are controlled

with epinephrine or neosynephrine subcutaneously or intravenously and amyl nitrite inhalation. Intramuscular injection of epinephrine in oil may be an aid for sustained effect.

SURGICAL CONSIDERATIONS

Approximately 10 per cent of adrenal medullary tumors are bilateral. In a fair proportion of cases it is impossible to ascertain either from clinical signs or diagnostic technics on which side the tumor is present. These factors lead us to favor a bilateral, simultaneous exploration of the adrenals. In sympathectomy for essential hypertension exploration of the adrenals is achieved by either splitting the diaphragm radially for a short distance or, recently, by pushing the diaphragmatic attachments off the vertebral bodies to a degree sufficient to expose the retroperitoneal tissues. In cases in which one suspects an adrenal tumor and is not contemplating sympathectomy, a technic comparable to that described by Young[18] is advocated. This permits bilateral, simultaneous exposure of both adrenals through separate retroperitoneal incisions. In order to shorten the operative time and achieve really simultaneous exploration it has been our custom to utilize two surgical teams. The patient is placed in a prone position upon the operating table. Paravertebral incisions are made about 6 to 8 cm. lateral to the spinous processes, centering the incision just below the twelfth rib. The latissimus dorsi musculature is divided in the line of the incision, exposing the serratus posticus inferior muscle which in turn is divided in its lower portion. The conjoined portion of the lumbodorsal fascia is incised just lateral to the sacrospinalis musculature and the retroperitoneal tissues exposed. The costovertebral ligament of the twelfth rib may be incised and the rib retracted upward for greater exposure. If necessary for a large tumor, some of the twelfth rib may be resected. The retroperitoneal fat is stripped off, thereby exposing Gerota's fascia which envelops the kidney and adrenal. An opening is made in Gerota's fascia over the adrenal, permitting its delivery and complete exploration.

Surgical Results. Data for the results listed in Table v are taken from the reviews of Biskind, Meyer and Beadner[15] (1939), MacKeith[1] (1943) and all cases reported since 1943, including the three added in this paper. Since 1943, twenty-four cases have been reported (including ours). Although three of these patients died during operation for adrenal tumor, four died who were not treated surgically; two patients unsuspected of having pheochromocytoma died during or shortly after operation for other conditions.

TABLE V
SURGICAL RESULTS

Dates	No. Cases	Successful (per cent)	Fatal (per cent)
1929–1936	19	12 (63)	7 (37)
1936–1943	18	15 (84)	3 (16)
1943–1947	20	17 (85)	3 (15)

Follow-up. Those patients who survived operation and the postoperative period have had full recovery from their paroxysms. Preoperative pathologic changes referable to sustained hypertension regressed with the re-establishment of persistent normal blood pressure. Some patients have been followed from seven to ten years.[19] The outcome has not been so favorable in the rare cases in which the adrenal tumor was malignant.

Between January, 1944 and December, 1946, three patients with pheochromocytoma were seen at the Stanford Hospital and Stanford University Medical School Out-Patient Clinics.

CASE REPORTS

CASE I. Mrs. J. C., a twenty-three year old white housewife, had a negative medical history until the onset of her present illness in December, 1943. She was seen in a prenatal clinic in September with a normal eight-weeks' pregnancy. Blood pressure readings were 100/60 to 105/70 on three occasions from October to December. On December 22nd, after some nose-bleeding,

the pressure was 200/120 to 220/130. There was moderate albuminuria and toxemia of pregnancy seemed likely. A Cesarean section was performed in another hospital in early January, 1944, but because the blood pressure remained high the patient entered Stanford Hospital on the clinic service January 21st. Physical findings included a blood pressure of 250/140, papilledema, retinal hemorrhages, narrowed retinal arteries, moderate enlargement of the heart to the left and an apical systolic murmur.

Laboratory findings were as follows: Blood counts were normal. Timed urine specimens were fairly constant: specific gravity, 1.010; pH, 7.0; protein, 1.2 Gm./24 hours; red blood cells, 3,000,000; white blood cells, 3,000,000; hyaline casts, 100,000; granular casts, 300,000. Repeated fasting blood sugars were from 95 to 100 mg. per cent. Spinal fluid, serum proteins, urea, creatinine and chlorides were repeatedly normal. X-rays of the skull, chest and abdomen, and excretory pyelograms were negative.

Differential diagnosis included malignant hypertension of unknown cause, placental neoplasm and intracranial lesion.

Dilatation and curettage recovered only normal placental remnants. On January 25th she had an intracranial hemorrhage followed by restlessness, headaches, epigastric distress, back pain and further diminution of vision. There were no typical paroxysmal increases of blood pressure although these symptoms were occasionally accompanied by a moderate rise from the usual range of 230/130 to 260/160. Continuation of the listed complaints led to a splanchnic section on February 16th. During this operation the adrenal glands were not explored. Operative and postoperative hypotension was controlled essentially with neosynephrine injections. The lowest pressure of this time was 114/98, and it rose to 200/120 within three days after operation. Adrenal pheochromocytoma was first considered after prompt restoration of hypertension. The patient had a fatal cerebral hemorrhage on March 17, 1944, only three months after the first signs of high blood pressure.

Autopsy revealed that the pheochromocytomas were small, bilateral, intra-adrenal; that on the right, 3.5 by 1.7 cm., replaced almost the entire gland. Generalized arteriosclerosis was present. The heart was 340 Gm., the left ventricle was 20 mm. thick and the coronary arteries were patent but contained atheromas. The brain revealed a recent hemorrhage into the pons, cerebral peduncle and fourth ventricle. The liver and kidneys showed no changes typical of toxemia of pregnancy but the kidneys were altered by the hypertension; small renal arterioles showed marked hyaline thickening of their subintimal layers, with fatty degeneration and poor cellular detail; the slightly larger arterioles had reduplication of the inner elastic membrane. The ascending arch and the thoracic and abdominal portions of the aorta had marked atheromatous changes with plaques 2 to 3 mm. thick. There were small plaques in the renal arteries.

Comment. This patient presented not only the usual diagnostic problem of sustained hypertension in a young person but added the tempting consideration of its relation to her pregnancy. As the first of the series she did not have the benefit of adrenal exploration at the time of splanchnicectomy; since she was of the 10 per cent group who had bilateral pheochromocytomas, the importance of the oversight may be questioned although the left tumor was small and the cortex there was not affected. It is of considerable interest that she had so much arteriosclerosis and left ventricular hypertrophy with hypertension of only three months' duration.

Case II. Mrs. E. P., a thirty-two year old white housewife, had a negative past medical history except for suspected hyperthyroidism in 1935 when she had a mild tremor and a blood pressure of 130/80. In December, 1944 she entered another hospital at term and in labor; her blood pressure was 210/155. Following a normal delivery, the blood pressure was 125/85 but soon returned to high levels which were uninfluenced by the usual medical treatments. There was mild to heavy albuminuria. As an out-patient during the next two months she continued to have marked hypertension, tachycardia, nervousness and headaches; the basal metabolism rate was +19 to +43, with normal blood cholesterol levels. Her ocular fundi showed evidence of slight bleeding and exudation and she had an episode of moderate left heart failure. Subtotal thyroidectomy in March, 1945 failed to reduce the basal metabolism rate or alleviate her symptoms. Because of severe left ventricular

failure, she was sent to Stanford University Hospital where she was admitted on the clinic service April 21st. Examination confirmed the changes in the retinae, the blood pressure was 170/140 to 140/110, the heart was enlarged and there was a loud systolic precordial murmur with gallop rhythm and pulmonary congestion. The cardiac status improved with therapy but the moderate left failure persisted and fresh retinal hemorrhages appeared during the next two to three weeks.

Laboratory examination revealed the following: Blood was normal; urine: specific gravity was 1.012 to 1.010, and there was 0.69 to 6.9 Gm. albumin in the twenty-four-hour specimens on repeated tests. Fasting blood sugar levels were 121, 131 and 160 mg. per cent; urea, 15 to 18 mg. per cent; chlorides 530 mg. per cent; cholesterol, 204 mg. per cent and plasma proteins, 5.8 Gm. per cent. The basal metabolic rate was +40. X-rays showed enlargement of both right and left ventricles of the heart, an enlarged left auricle and full pulmonary conus; excretory pyelograms were normal. Repeated electrocardiograms were taken; the only significant finding was a marked left axis deviation that shifted toward normal after the patient's operation.

Differential diagnosis considered the relationship of the hypertension to a post-toxemic complication, a primary renal lesion, retained placental tissue, the problem of an intrinsic myocardial affection and cardiac disease dependent upon thyrotoxicosis.

The blood pressure fluctuated from 140/110 to 170/130, with occasional increasing nervousness, tachycardia and perspiration but no clearly recognized attacks of paroxysmal hypertension. By May 19, 1945, the cardiac failure was sufficiently controlled to allow a bilateral splanchnicectomy and exploration of the adrenals

After anesthesia was established with intratracheal ether and oxygen the patient was turned to the prone position and at once sank into profound shock which was corrected with whole blood transfusion and neosynephrine injections. Bilateral incisions allowed simultaneous operative procedure but the right adrenal gland was first exposed and, because it was definitely enlarged, three-fourths of it was excised before the left gland was examined. The left adrenal contained an unmistakable tumor which was removed, leaving about one-third of the unaffected gland *in situ*. Routine bilateral splanchnicectomy was then performed. Pathologic examination of the adrenals showed that the tissue from the right gland was normal while the left contained a typical pheochromocytoma. Adrenal cortical extract in large amounts was given intramuscularly during the operation and routinely for nine postoperative days. Neosynephrine and epinephrine in oil supplemented against hypotension. The blood pressure was 160 to 180 systolic at the start of operation; it dropped to 80 during the mentioned period of shock and rose to 170 at one point during the procedure. The blood pressure stabilized in the range of 95/50 to 110/80 postoperatively and was 100/75 at dismissal five weeks later. Signs of cardiac failure cleared steadily.

When the patient was last examined in May, 1946, one year after her operation, the blood pressure was 110/85, the ocular fundi showed no retinopathy and there were no heart murmurs or evidences of cardiac enlargement. In correspondence in August, 1947 she stated she had felt quite well to date.

Comment. This patient's history again raised the problem of the relationship between her hypertensive state and possible toxemia of pregnancy. The elevated basal metabolic rate and diagnosis of moderate hyperthyroidism ten years earlier required consideration of thyrotoxicosis; absence of other evidence of thyroid disease and the probability that the basal metabolic rate was affected by her cardiac failure were against this. Other reviews have cited instances in which a greatly hypertrophied adrenal gland has been mistaken for an adrenal tumor. The satisfactory course for over two years postoperatively suggests that the patient is completely relieved of her hypertensive state. Splanchnicectomy must be considered in evaluating her course.

Case III. E. G., a twenty-six year old white physician, was seen on November 13, 1946, with the complaint of "paroxysmal hypertension" of two-years' duration. His past history included chronic frontal sinusitis treated surgically and paroxysmal auricular tachycardia since the age of ten. The latter had been proved by electrocardiogram, was readily controllable and was clearly distinguished by the patient from the attacks described in his present com-

plaint. Two years previously he had first noted episodes of sudden tenseness, nervousness, tachycardia and palpitation associated with tremor and profuse perspiring as the attacks subsided after two to five minutes. There was pupillary dilatation during some attacks but blanching or pallor of the skin was not noted. There were no recognized provocative factors except that attacks had occurred occasionally when he rolled over in bed. Attacks increased in frequency from one every two to three weeks to one or more almost daily; they varied in intensity and duration. An episode in June, 1946 initiated a violent headache. Subsequent attacks were associated with similar occipital pain, often too severe to be eased by narcotics and which lasted five minutes to fourteen hours after the paroxysm had ceased. Complete neurologic study, including skull films, electroencephalogram and cerebrospinal fluid examination, showed no evidence of an intracranial lesion.

While stationed at a U. S. Naval hospital in the following three months, the patient thoroughly studied his case. His usual blood pressure varied from 130/70 to 150/90, but when taken during several typical attacks it was in the range of 200 to 220/110. The following examinations were normal: blood count, urinalyses, serology, serum cholesterol, glucose tolerance, cold pressor test, electrocardiogram, x-rays of skull, chest, sinuses and excretory pyelograms. Blood sugar levels during attacks were variable. Intravenous insulin, 0.1 unit per Kg. body weight, reduced the fasting venous sugar from 78 to 44 mg. per cent, caused a moderate insulin reaction but did not induce a paroxysm. Epinephrine, 0.2 cc. of 1:100,000 intravenously caused symptoms precisely simulating those in an attack. The basal metabolic rate was +3 and +8 on two tests.

He entered Stanford Hospital in November, 1946, for confirmation of his own diagnosis of pheochromocytoma. Physical examination revealed a husky and apparently healthy young man. The retinae were normal, the lungs clear, the heart normal in size, regular and without murmurs. Blood pressure readings varied from 130/90 to 180/110. The abdomen was normal and massage of the belly and flanks did not produce an attack. No severe paroxysms occurred spontaneously during this period. X-rays and other studies were repeated and found normal. The twenty-four-hour excretion of 17-ketosteroids was 30 mg. The patient was disinclined to submit himself to the intravenous injection of histamine.

On the basis of the objectively studied attacks, and the lack of evidence of sustained hypertension, hyperthyroidism, polyglandular or Cushing's disease or brain tumor, the preoperative diagnosis of pheochromocytoma seemed justifiable. For three days preoperatively he was given a high salt diet with 4 Gm. of additional salt by mouth. Desoxycorticosterone, 5 mg., was administered intramuscularly the day before and the day of operation. Adrenal cortical extract, 5 cc., was given intramuscularly during the surgical procedure and was repeated immediately postoperatively.

Operation was performed on December 3, 1946, using a bilateral paravertebral approach to the adrenals; we had two surgical teams. Anesthesia used was tribromethylene rectally for induction, followed by intratracheal nitrous oxide and ether. A pheochromocytoma of the right adrenal gland was found that weighed 24.5 Gm. and had perforated the cortex, which was not greatly altered and was left *in situ*. The left adrenal was normal. Blood pressure fluctuations during the operation were controlled with injections of neosynephrine, epinephrine and epinephrine in oil; amyl nitrite inhalations were given without noticeable effect when the tumor was manipulated. The initial blood pressure was 180/100, and there was no period of alarming shock. When the tumor was handled, the systolic pressure rose to above 300 mm. mercury and the diastolic pressure was 260. Immediately after clamping the veins of the tumor pedicle the blood pressure dropped to 120/80. It then stabilized at 130/80 to 150/100. Adrenal hormonal therapy was not necessary postoperatively.

He has been seen as late as two years since his operation and reports no further attacks. His blood pressure is usually 130/70 when taken quietly at home but rises as high as 160/90 when he is examined in the office. He reports that he blushes at slight provocation since the tumor was removed whereas he had been previously untroubled in this way.

Comment. This patient suffered classical paroxysms of the "adrenal-sympathetic syndrome," and after excluding an intracranial cause for his violent headaches, by his own objective observations he was able to decide that he probably had a pheo-

chromocytoma. Completely negative results in an array of special laboratory and x-ray examinations substantiated his conclusion and justified the preoperative diagnosis on a purely clinical basis. He still has moderate vasomotor instability which has been noted in other cases.

COMMENT

Pheochromocytomas are being diagnosed preoperatively with increasing frequency. The importance of the diagnosis is greater now that the operative risk has been reduced by proper medical preparation and aid during the surgical and postsurgical periods and by added anesthetic and surgical experience. Hypertension, paroxysmal or sustained, caused by pheochromocytoma is promptly corrected by excision of the tumor; the effect is apparently lasting. The possibility of the presence of adrenal medullary tumor should be considered whenever the problem of hypertension is presented, and exploration of the adrenal glands should be part of every operation undertaken for the relief of hypertension. The use of new procedures such as the intravenous injection of histamine or the benzodioxane drugs may make the diagnosis simple and certain; experience with these tests is limited at present, and in cases of very high blood pressure they may be dangerous. Since all other tests, including x-rays, may be negative in the presence of pheochromocytoma, clinical observation remains the best guide.

SUMMARY

The clinical syndrome associated with tumors of the adrenal medulla (pheochromocytoma) is discussed with reference to the recorded experience in diagnosis and treatment. Three new cases at the Stanford University Hospital and Clinics in a two-year period are presented.

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Treatment of Pernicious Anemia with Crystalline Vitamin B_{12}*

RANDOLPH WEST, M.D. *and* EDWARD H. REISNER, JR., M.D.
New York, New York

SINCE the initial publications recording the isolation from liver of crystalline vitamin B_{12},[1] and a positive hematologic response[2] in Addisonian pernicious anemia following the injection of microgram doses, several confirmatory reports have appeared. These and the various steps leading to the discovery of B_{12} have been summarized well in a recent editorial.[3] E. L. Smith[4] isolated similar crystals from liver, announced that they contained cobalt, nitrogen and phosphorus and suggested a molecular weight of 1,670 for the compound. Rickes et al.[5] have found that vitamin B_{12} contains these elements but no sulfur. Material with the same growth-promoting properties as B_{12} has been isolated from other sources[6] but the crystalline substance as yet has been recovered only from liver.

This paper reports eleven cases of Addisonian pernicious anemia treated parenterally with crystalline vitamin B_{12}, including the three original cases.[2] All have shown hematologic improvement, with blood counts rising to normal levels when weekly doses of 25 micrograms or less were injected. The minimal effective dose has been found to be 1 microgram a day, intramuscularly. Five patients with spinal cord lesions (Cases IV, VIII, IX, X and XI) have shown varying degrees of improvement; none has become worse, as has happened at times in treatment with pteroyl glutamic acid.[7] All of these patients with spinal cord lesions are walking readily today. The effect of vitamin B_{12} on the cord lesions of pernicious anemia appears promising but only a preliminary opinion can be given at this time. The effective oral dosage of vitamin B_{12} is being studied at other clinics.

Material Studied. All of the patients had classical Addisonian pernicious anemia with achlorhydria after histamine, a negative gastrointestinal x-ray, a typical blood picture and a megaloblastic bone marrow smear. All patients with spinal cord lesions had normal spinal fluids. While under study, the patients were on diets free from liver, kidneys or glandular meats and received no liver extract, folic acid or vitamin preparations.

CASE REPORTS

CASE I. A sixty-six year old female was admitted to Kings County Hospital because of progressive weakness, fatigability, anorexia and nausea of two months' duration. The positive physical findings on admission included pallor of the skin and mucous membranes, flame-shaped hemorrhages in the eye grounds and signs of mild congestive heart failure. The neurologic examination was normal. The blood count on admission was 1,500,000 with 4.00 Gm. of hemoglobin. Reticulocytes were 0.4 per cent. Five days after a single intramuscular injection of 0.15 mg. of vitamin B_{12} there was a reticulocyte response of 27 per cent. The blood count rose steadily to 4,500,000 six weeks after this one injection. (Fig. 1.)

CASE II. A fifty-four year old male had noticed progressive weakness, pallor, dyspnea and precordial pain on exertion for one month prior to admission to the First Medical Division of Bellevue Hospital. The positive physical findings included pallor, lingual atrophy, slight enlargement of the heart with signs of mild congestive heart failure, a smooth liver enlarged 3 cm. below the rib margin, a palpable spleen tip and sluggish deep reflexes. There was no

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, and the Fourth Medical Division (New York University), Bellevue Hospital, New York.

impairment of vibratory or position sense. The admission blood count was 1,420,000 with 6.5 Gm. of hemoglobin. There were 2.8 per cent reticulocytes. Five days after a single intramuscular injection of 0.006 mg. of vitamin B_{12} the reticulocytes reached a peak of 26 per cent.

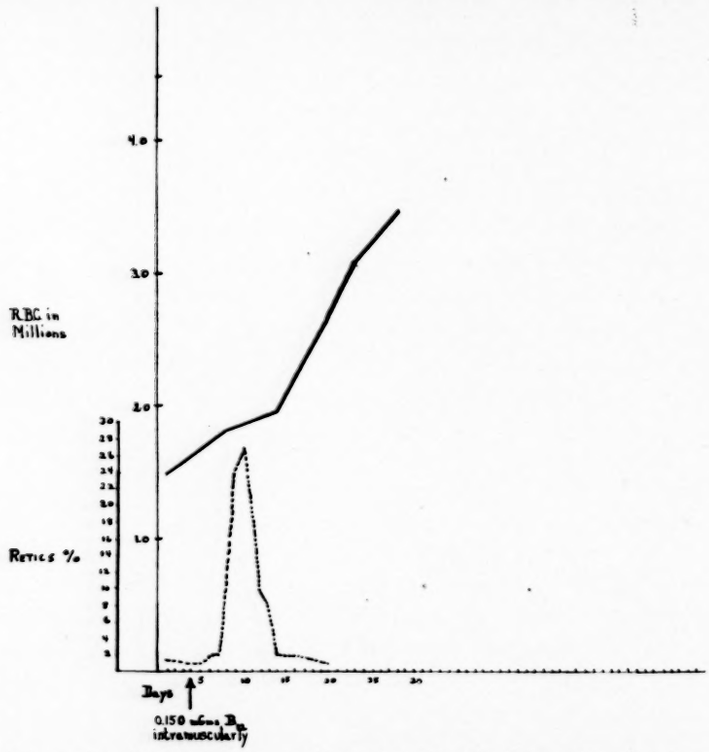

FIG. 1. Case I. A sixty-six year old white female with pernicious anemia who had a maximal reticulocyte response of 27 per cent five days after a single injection of 0.150 mg. of vitamin B_{12}. She was transferred to another hospital where her count was reported to be over 4 million without any additional therapy.

A second injection of 0.50 mg. of B_{12} was given two weeks after the first one. The red blood cell count was 4,750,000 sixty-four days after the start of treatment. Two months later it was still 4,500,000. (Fig. 2.)

CASE III. A sixty year old woman was admitted to the Fourth Medical Division of Bellevue Hospital in a semi-comatose, confused state. For twelve years she had been a semi-invalid and had taken various forms of non-specific anti-anemic therapy. For a month prior to admission she had been growing progressively weaker and had complained of soreness of the tongue and numbness of the fingers and toes. On the day before she entered the hospital she ate several pounds of liver because she was told it would help her. On admission she was found to be weak and pale with a lemon colored hue to the skin, atrophy of the tongue, enlargement of the heart and liver and slight diminution of the vibratory sense below the knees. Position sense and deep tendon reflexes were normal. Her mental state was quite confused with alternating periods of euphoria and paranoia. The blood count was 1,340,000 with 5.8 Gm. per cent of hemoglobin. There was a spontaneous rise of reticulocytes to 7.8 per cent four days after admission, attributed to the ingested liver. When the reticulocytes had dropped to 2.2 per cent, a single injection of 0.003 mg. of vitamin B_{12} was given. This induced a reticulocyte rise to 10.4 per cent and rapid regeneration of red blood cells. Ten days later an injection of 0.05 mg. of B_{12} was given. With no additional therapy, the blood count rose to 4,070,000 thirty-five days after the start of treatment. There was an accompanying gain of strength and appetite and less mental confusion but ideas of reference persisted and she was transferred to the psychiatric service. (Fig. 3.)

CASE IV. A sixty-nine year old laboring man had been admitted to the Fourth Medical Division of Bellevue Hospital on five previous occasions for hypertensive heart disease, chronic pulmonary tuberculosis, chronic alcoholism and, in 1947, pernicious anemia which responded to folic acid therapy with an 18 per cent reticulocyte rise. Following this admission he failed to continue therapy and gradually lost strength in early 1948. For a month prior to the present hospitalization he had a severe cough, anorexia, vomiting and dyspnea. For the last two weeks he had been too weak to leave his room and had subsisted mainly on coffee. On physical examination he was acutely and chronically ill, with a temperature of 101°F. There was dyspnea and orthopnea, pallor, lingual atrophy and pulmonary emphysema. Moist and crackling rales were heard in the left lower lobe. The heart was enlarged to the left and the liver was palpable 3 cm. below the costal margin. There was absent vibratory sense in both forearms and legs and diminished sensation to pin-prick in the same areas. The deep reflexes in the lower extremities were diminished as was also the position sense in the toes. The blood count on admission was 2,700,000 with 9.8 Gm. per cent of hemoglobin and 1.6 per cent reticulocytes. The chest x-ray revealed chronic fibroid phthisis with superimposed pneumonitis of the left lower lobe which gradually cleared under symptomatic treatment. Sputum culture was positive for tuberculosis. The patient was given a daily intramuscular injection of 0.001 mg. of vitamin B_{12}. On the ninth day of treatment the reticulocytes were 10.4 per cent. The blood count rose gradually and reached 4,470,000 after fifty-three days during which time there was rapid subjective improvement and relief of symptoms. Neurologic examination now showed

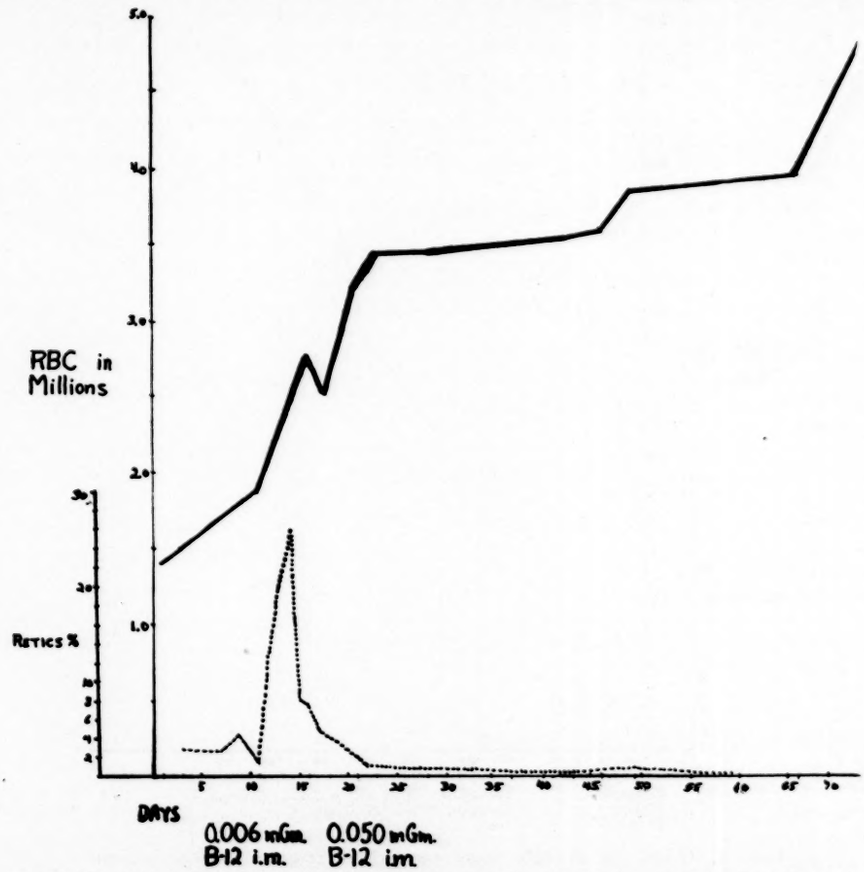

FIG. 2. Case II. A fifty-four year old white male with pernicious anemia who showed a maximal reticulocyte response of 26 per cent five days after a single injection of 0.006 mg. of vitamin B_{12}. A second injection of 0.050 mg. sent the blood count to 4,750,000 sixty-five days after the onset of therapy.

normal pin-prick, vibratory and position sense and active deep tendon reflexes. The patient was placed on liver extract and transferred to the tuberculosis service.

CASE V. A seventy-five year old woman with known pernicious anemia since 1937 was unable, because of crippling arthritis, to come for liver injections and, therefore, was admitted to the Fourth Medical Division of Bellevue Hospital in relapse for the fourth time in June, 1948. On admission there was a marked glossitis, pallor of the skin and mucous membranes, dilatation of the heart, signs of mild congestive heart failure and extensive osteoarthritis. Except for a moderate diminution of vibratory sense below the knees, the neurologic examination was normal. The blood count was 1,810,000 with 8.5 Gm. per cent of hemoglobin and 0.8 per cent reticulocytes. Vitamin B_{12} was started in daily intramuscular doses of 0.0001 mg. After a week of this dosage with no effect on the blood or reticulocyte levels the daily dose was increased to 0.0075 mg. A sub-maximal reticulocyte response of 7 per cent on the seventh day of this therapy was associated with extremely rapid regeneration of erythrocytes. (Table I.)

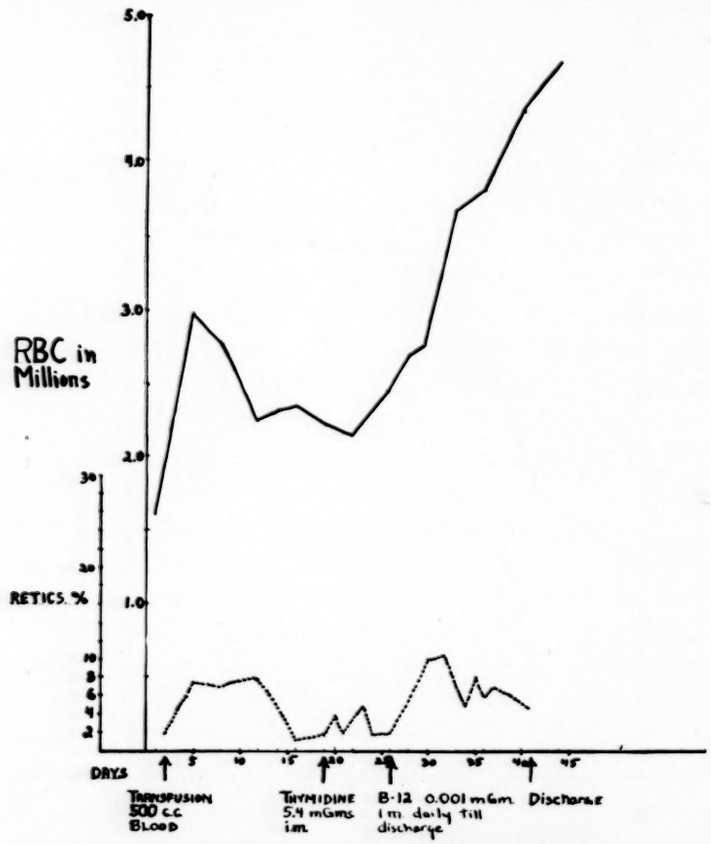

FIG. 3. Case VII. A fifty year old white female had pernicious anemia. Following a transfusion on admission, there was a spontaneous reticulocyte rise which persisted for two weeks. At this time she received 5.4 mg. of thymidine. One week later she was given 0.001 mg. of vitamin B_{12} intramuscularly daily for fifteen days.

After twenty-three days of this dose a single injection of 0.0125 mg. produced no further reticulocyte rise, indicating complete previous response. The blood count rose rapidly to 4,400,000 at which time the patient was discharged thirty-two days after beginning B_{12} treatment on a dose of 0.0075 mg.

CASE VI. A forty-one year old man had noticed increasing weakness, anorexia and weight loss for six months. For six weeks he had noticed dyspnea and anginal pain on exertion and after meals. On admission to the Fourth Medical Division of Bellevue Hospital the positive physical findings included pallor and a

TABLE I

VITAMIN B_{12} IN PERNICIOUS ANEMIA

Patient, Hospital*	Sex	Age	Reticulocytes		Red Blood Cells (millions)												Type of Treatment Administered
			Peak Per Cent	Day of Peak	At Start of Treatment	Day of Treatment											
						1	5	10	15	20	25	30	35	40	50	60	70+	
I-KC	F	66	27	5	1,5	...	1,8	1,9	2,6	...	3,3	...	...	...	...	...	...	0.150 mg. B_{12} i.m.‡
II-B	M	54	26	5	2,0	1,5	1,9	2,5	3,4	3,4	...	3,1	3,4	3,7	...	3,9	4,7	0.006 mg. B_{12} i.m. on 3/3/48 0.050 mg. on 3/16/48
III-B	F	60	10.2	4	1,7	1,6	2,1	2,5	2,6	3,0	3,2	3,5	4,0	...	...	...	...	0.003 mg. B_{12} i.m. on 3/1/48 0.050 mg. on 3/10/48
IV-B	M	69	10.4	9	2,4	2,4	2,7	2,9	3,2	3,4	3,5	...	3,9	3,8	4,4	...	...	0.001 mg. B_{12} i.m. daily for 47 days
V-B	F	75	7	7	2,3	2,3	2,3	2,3	2,9	3,1	3,4	3,4	3,6	4,2	...	...	...	0.0001 mg. B_{12} i.m. daily 6/14/48–6/20/48 0.00075 mg. i.m. daily 6/21/48–7/8/48 0.0125 mg. in a single injection 7/14/48
VI-B	M	41	13.4	8	1,3	1,3	1,5	1,9	2,3	2,2	2,5	2,9	3,3	4,5	...	...	...	0.0005 mg. B_{12} i.m. daily 6/21/48–7/12/48 0.0125 mg. B_{12} in a single injection 7/14/48
VII-B	F	50	10.4	4	2,4	2,4	2,7	3,3	4,2	...	...	...	...	...	...	...	...	Transfusion 500 cc. 7/9/48 Thymidine 5.4 mg. i.m. 7/26/48 0.001 mg. B_{12} i.m. daily 8/2/48–8/17/48
VIII-P	F	48	....	..	3,4	3,4	...	3,8	...	...	4,4	...	...	4,1	...	...	...	0.025 mg. B_{12} i.m. weekly from 7/21/48
IX-P	F	50	29.1	5	1,6	1,6	...	3,0	3,6	3,7	...	3,9	...	...	5,1	...	5,7	0.150 mg. Co as $CoCl_2$ i.m. 7/2/48 negative 0.025 mg. B_{12} i.m. weekly from 7/9/48
X-P	M	57	14.0	8	3,3	3,3	...	3,9	...	...	4,1	...	3,7	3,7	...	4,7	...	0.025 mg. B_{12} i.m. weekly
XI-P	M	44	9.2	6	2,5	2,5	...	...	...	...	...	4,3	...	...	...	4,6	5,2	0.010 mg. B_{12} then 0.025 mg. B_{12} i.m. weekly

* KC = Kings County; B = Bellevue; P = Presbyterian.

† Or later.

‡ Intramuscularly.

lemon yellow hue to the skin, lingual atrophy, a systolic apical murmur in the heart and a liver edge palpable 3 cm. below the costal margin. Neurologic examination was normal. The blood count was 1,460,000 with 6.0 Gm. per cent of hemoglobin and 0.6 per cent reticulocytes. He was given a daily intramuscular injection of 0.0005 mg. of vitamin B_{12} for twenty-one days. On the eighth day there was a sub-maximal reticulocyte response of 13.4 per cent. On the twenty-second day a single dose of 0.0125 mg. of B_{12} was injected which was followed by a reticulocyte response of 10.4 per cent six days later. With no further treatment, the blood count reached 4,500,000 forty-six days after the beginning of therapy and the patient was discharged, free from symptoms.

Case VII. A fifty year old white female with pernicious anemia diagnosed two years previously had taken liver injections until six months before admission. For the last two months there had been gradually increasing weakness and dyspnea. For four days she had had acute weakness, dyspnea, orthopnea and dependent edema. On admission to the Fourth Medical Division of Bellevue Hospital the patient was acutely ill with congestive heart failure. The heart was enlarged to the left with signs of mitral stenosis. The liver was palpable 8 cm. below the costal margin. Neurologic examination, done after the patient was compensated, was normal. The blood count on admission was 1,610,000 with 7.0 Gm. per cent of hemoglobin. She was given a transfusion of 500 cc. of whole blood on admission which brought about a spontaneous reticulocyte rise up to 8 per cent. The heart failure was treated with oxygen, digitoxin and mercurial diuretics and no specific anti-anemic therapy was given until eighteen days after admission. At this time her blood count was 2,210,000 and reticulocytes were 2.0 per cent. An intramuscular injection of 5.4 mg. of thymidine was given without significant effect on the blood picture. On the twenty-sixth hospital day daily injections of 0.001 mg. of B_{12} were begun. There was a prompt reticulocyte rise to 10.6 per cent five days later. The red blood cell count rose remarkably rapidly and reached 4,550,000 eighteen days after the start of B_{12} therapy. There was complete relief of symptoms of heart failure at this time and the patient was discharged.

Case VIII. A forty-eight year old woman had parasthesias of the extremities for three years and difficulty in walking for one year prior to admission to Presbyterian Hospital. For the last year she had amenorrhea. Positive physical findings on admission were limited to the neurologic system. There was diminished vibratory and tactile sensation in the hands and feet, positive Romberg, staggering gait, hyperactive deep reflexes and normal plantar reflex. The red blood count was 3,600,000 with 12.0 Gm. of hemoglobin. She was given 0.025 mg. of vitamin B_{12} every week for three months. The blood picture was restored to normal in a month and there was rapid return of strength and subjective improvement. At the end of five months of treatment neurologic examination revealed marked improvement in the Romberg test, definite improvement in gait and no change in the vibratory sense.

Case IX. A fifty year old housewife, who had suffered from soreness of the tongue and weakness and numbness of the legs for two months, was admitted to Presbyterian Hospital. Physical examination disclosed marked pallor, atrophy and inflammation of the tongue and vitiligo. Vibratory sense was absent below the knees, position sense was absent in the toes, reflexes were normal, there was no Babinski reflex and the Romberg test was slightly positive. Initial red blood cell count was 1,600,000 with 6.5 Gm. of hemoglobin; 150 micrograms of cobaltous ion (as chloride) was given intramuscularly with no hematologic response. A reticulocyte count of 29.1 per cent was recorded five days after an injection of .025 mg. of vitamin B_{12}. Thereafter, she received a similar dose of B_{12} weekly. The blood picture returned to normal at the end of six weeks and there was accompanying subjective improvement. After four months the Romberg test was negative; position sense was improved but vibratory sense was still diminished to absent in the lower extremities.

Case X. A fifty-seven year old white man had been treated for pernicious anemia for three years. During the first two years he was treated by a doctor with both liver extract injections and oral folic acid. For the last year the patient had treated himself with folic acid, taking about 3,000 mg. by mouth in that time. Two weeks before his admission to Presbyterian Hospital he noticed paresthesias of the hands and feet and an unsteady gait. The positive physical findings were absent vibratory and position sense in the lower extremities, normal

Babinski, deep tendon reflexes and a markedly positive Romberg. The red blood count was 3,300,000 with 11.0 Gm. of hemoglobin. There was an excellent hematologic response to .025 mg. weekly of vitamin B_{12} with accompanying clinical improvement. (Table I.) After 3 months of treatment the Romberg test was questionably positive and there was marked improvement of gait but vibratory sense was still absent below the knees.

CASE XI. A forty-four year old white male had complained of impotence, leg paresthesias and difficulty in walking for six months. Recently he had noticed clumsiness and numbness of the hands. Four days before admission to Presbyterian Hospital he developed a productive cough and fever. On admission he was acutely ill with signs of consolidation of the left lower lobe. The neurologic examination showed a strongly positive Romberg, absent vibratory sense in the lower extremities and a Babinski reflex on the right side. The initial blood count showed 2,500,000 erythrocytes, 8.5 Gm. of hemoglobin and 9,000 leukocytes. The sputum contained Streptococcus viridans and Hemophilus influenzae. After two weeks of penicillin therapy his temperature returned to normal. He was given an initial dose of 0.010 mg. of vitamin B_{12} and .025 mgs. weekly thereafter. The blood count returned to normal rapidly. (Table I.) After seven months the Romberg test was slightly positive, there was no Babinski reflex and vibratory sense was still absent from the lower extremities. When last seen the patient's gait was steady and he felt well.

COMMENTS

The discovery of cobalt in vitamin B_{12} is of great interest because that element had previously been implicated in hematopoiesis. The available literature on this subject has been summarized by several authors.[8,9] The salts of the metal alone given to one of our patients (Case IX) were without effect. Studies with salts of radioactive cobalt have shown that after parenteral injection they are recoverable in part in the stomach contents of cattle[10] and are stored in greatest concentration in the liver, pancreas and kidneys, respectively. Cobalt must enter the body from without, but there is no parallelism between the cobalt content of foods and their content of extrinsic factor, as shown in a study by Morris.[11]

The question will be raised at once where B_{12} fits into our present knowledge of hematopoiesis and what relationship it bears to two other crystalline substances with antipernicious anemia activity, thymine[12] and pteroyl-glutamic acid.[13]

Thymine can replace folic acid in the growth requirements of certain bacteria in a ratio of 3,000:1.[14] Thymine in the same high proportions (12 to 15 Gm. per day) will maintain patients with pernicious anemia in hematologic remission but, like folic acid, it has no favorable effect on the cord lesions of that disease.[15] From this it appears that folic acid may act as a coenzyme in the metabolism of thymine. Wright et al.[16] have reported that thymidine (thymine desoxyriboside) in comparatively high concentrations can replace vitamin B_{12} in the growth of Lactobacillus lactis and conclude that vitamin B_{12} may function as a coenzyme in the conversion of thymine to thymidine. Thymidine (5.4 mg.) given to the patient in Case VII produced a rise in reticulocytes from 2.0 to 5 per cent but caused no significant change in the blood level. With the subsequent administration of 1 microgram a day of vitamin B_{12}, the blood count returned to normal in fifteen days.

CONCLUSIONS AND SUMMARY

1. Eleven patients with Addisonian pernicious anemia have been treated with crystalline vitamin B_{12}. All have shown complete hematologic remission. Five patients with combined system disease have shown marked improvement in their neurologic condition.

2. The effective parenteral dose has been found to be slightly less than 1 microgram of crystalline vitamin B_{12} a day.

3. The current status of our knowledge of the relationship of thymine, folic acid, cobalt and vitamin B_{12} is discussed.

4. It would appear that vitamin B_{12} is probably the erythrocyte maturation factor of liver.

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Seminars on Congestive Failure

Cardiac Venous Congestion*

Its Causes and Consequences

JOHN MCMICHAEL, M.D., F.R.C.P.
London, England

"If then, Socrates, we find ourselves in many points unable to make our discourse . . . in every way wholly consistent and exact, you must not be surprised. Nay, we must be well content if we can provide an account not less likely than another's."
Plato, "The Timaeus"—A. E. Taylor's Translation

THE straightforward idea that blood is dammed up in the veins behind a failing heart and that, in consequence, fluid leaks from the capillaries under pressure has an attractive simplicity. The vital machinery of the body, however, is much more complex, and this simple view is no longer adequate to explain all the observable phenomena.

There is a good deal of loose thinking concerning the way in which an increase or a decrease in cardiac output reacts on the venous pressure. It is commonly remarked that when the cardiac output increases the venous pressure falls, as though the blood were lifted out of the venous system and transferred into the arteries. It is clear, however, that the rate of removal of blood from the central end of the veins must equal the rate of inflow into the veins at the peripheral end. The volume of blood within the veins will thus remain unchanged. There is no fundamental reason, therefore, why an increased minute volume of the circulation should make any difference to the general venous pressure unless the capacity of the venous system is changed by some alteration in tone of the vein walls.

The pressure *gradient* in the veins, however, may alter with an increase in cardiac output, a higher pressure occurring at the peripheral end of the venous system and a lower pressure at the centre. In heart failure, with decreasing blood flow, diminution of the pressure difference between peripheral and central veins is a natural consequence.[25,48] Numerous instances can be quoted in which acutely produced changes in cardiac output are not accompanied by simple consequential changes in the central venous pressure. The following may be cited as examples: (1) Adrenaline has been shown to increase the cardiac output in normal man without significant change of venous filling pressure.[37] (2) Venous pressure changes induced experimentally usually influence the cardiac output in a parallel direction, i.e., a rise in venous pressure causes a rise in output, while the converse result occurs when the venous pressure is reduced (Starling's Law).[28,37,45]

It is therefore not justifiable to assume that increased minute volume of the circulation is necessarily accompanied by a passive fall in venous pressure. Should the venous pressure fall be primary, the cardiac output may well be reduced.

As a result of studies on cardiac output with the technique of cardiac catheterization it is now widely realized and accepted that the rise of venous pressure in heart failure is not a simple direct mechanical consequence of a low heart output at rest.[33,35,46,61] In the early stages of congestive heart failure the output of the heart is often within normal limits when the venous pressure is raised.[33,61] A large group of patients (emphysema, anemia, beri-beri, etc.) may present the phenomena of venous

* From the Department of Medicine, Postgraduate Medical School of London, London, England.

engorgement and accompanying oedema and yet have a high cardiac output.[35,46,61] In such patients the raised venous pressure cannot be the result of inadequate pumping of blood by the heart.

We are thus compelled to reconsider the whole problem of cardiac venous congestion along new lines. We have briefly mentioned the way in which change of cardiac output and blood flow may affect the gradient of venous pressure, and further consideration of the influence of a failing heart on the venous pressure will be outlined below.

The major factors influencing venous pressure are: (1) the tone of the vein walls and (2) the volume of blood within the veins. Of these the first is probably the more important physiologically, as it is more adaptable to rapid adjustment.

VENOMOTOR REGULATION*

The venous system can no longer be considered as a system of passive tubes leading blood back to the heart. It is a matter of common clinical experience to observe the contractile character of the veins. We have all made use of the tapping process in order to dilate a contracted vein, the so-called "Klopfversuch" of Goltz.[18] Similarly, in the terminal stages of heart failure, when the central veins in the neighbourhood of the heart are grossly engorged, everyone has had the experience of inability to find an arm vein sufficiently large for insertion of a needle.

In 1890 Roy and Sherrington[51] showed that "there are in the vago-sympathetic nerves descending fibres, section or stimulation of which can produce either a rise or a fall of the general venous pressure." Donegan[11] observed contraction of the veins of the legs in response to stimulation of the sciatic nerve. This contraction was apparently mediated by the sympathetic fibres carried in the nerve. In man, Lewis and Landis[29] observed dilatation of the veins of the arm and hand following sympathectomy, and this relaxation of the vein walls was shown to be independent of the local temperature. There is good evidence that these venomotor nerves are connected to a regulating centre closely associated with the other vasomotor regions in the central nervous system. Doupe, Krynauw and Snodgrass[12] were able to demonstrate constriction of an isolated section of an arm vein in man during exposure of the rest of the body to cold. Fleisch[14] and Gollwitzer-Meier and Bohn[17] showed that the inhalation of carbon dioxide brought about contraction of an isolated segment of vein with intact nervous connections but not exposed to the change in blood-gas content. Fleisch[15] was also able to demonstrate that a rise in pressure in the carotid sinus produced dilatation of the veins of the mesentery, while Charlier and Philippot[6] have recently demonstrated that reduction of pressure in the carotid sinus is accompanied by a rise in pressure in the right auricle with an increase in cardiac output in the dog.

An observation by Riml[49] is also of interest. When the pulmonary artery of a rabbit is tied and the cardiac drive to the circulation ceases, half the animal's blood volume may flow out of the veins near the heart when these are incised; prior to incision the pressure rises steeply. In the absence of any systolic ejection into the arteries, this rise of pressure in the venous system can only result from contraction of the veins and venules. This is probably another illustration of increased venomotor tone resulting from cutting off the cerebral blood supply.

These examples make it clear that the tone of the muscular walls of the veins is subject to venomotor regulation. The general rule which seems to underlie the venomotor reflexes in the data given above is that a rise of venous pressure occurs when there is need for a greater cerebral circulation and, conversely, a dilatation of the

* In this brief account of venous pressure regulation the influence of such mechanical factors as limb muscle movements and respiratory variations is omitted. These influences are of a transient nature and cannot play any part in the production of the sustained rise in venous pressure in heart failure.

veins and fall in venous pressure results when the pressure in the carotid artery is high, while the opposite occurs when the pressure is reduced. In these particular instances it would appear that the rise or fall of venous pressure may influence cardiac output in an appropriate direction, greater cardiac output being brought about when this is needed.

STARLING'S LAW OF THE HEART

The direct relationship between venous pressure and cardiac output (Starling's Law), implicit in the above remarks on venous pressure regulation, requires some further elaboration.

The principle established by Starling and his collaborators[40] was that the strength and magnitude of systolic ejection (stroke output) is dependent upon the length of the cardiac fibres in diastole. Although there was a general relationship between the filling pressure of the right auricle and cardiac output, Starling himself did not think that the diastolic fibre length was solely determined by the pressure within the ventricle at the end of diastole. His methods, however, were probably not adequate; and when Wiggers[67] re-studied the problem later, it was found that the diastolic filling pressure was, in fact, the decisive factor.

Starling's Law was, of course, worked out on isolated hearts freed from other influences, nervous and hormonal. The direct relationship between venous filling pressure and cardiac output has often been demonstrated in man.[28,37,45] Bleeding to a sufficient degree may reduce the cardiac output considerably while saline infusions may increase it.[37] The stroke output has been shown to vary with the "net filling pressure" accompanying the changes of the respiratory cycle.[45] Sometimes, however, the expected relationship between cardiac output and filling pressure may not be demonstrable in intact man.[64] This is scarcely surprising as the presence of other nervous and humoral controlling influences may make the maintenance of standard conditions of cardiac contractility impossible.

While there is considerable unanimity of opinion that the cardiac output is reduced when the diastolic filling pressure is low in various conditions of "shock,"[45] it is not at all clearly established that a rise in venous pressure is a primary factor in determining increased cardiac output under physiologic stress. In exercise, for example, it seems to be well established that the venous pressure may not rise much[63] and may even fall[27] while the heart may not enlarge significantly until the exercise becomes severe.[30] Thus the first mechanisms which bring about an increased cardiac output in health are probably cardioacceleration and increased emptying of residual blood from the ventricles.[30] There is now strong evidence that the ventricles do in fact contain blood at the end of a normal contraction. This has been demonstrated by a discrepancy between the heart volume and stroke output.[31,32] Lysholm and his collaborators found the average heart volume in normal recumbent subjects to be 630 cc. If we take a stroke output of 80 cc. from each ventricle, the heart volume at the end of systole will be 630 − 160, i.e., 470 cc. As the specific gravity of heart muscle is slightly greater than unity, the volume of the heart muscle is unlikely to exceed 300 cc. in a heart of normal weight. This leaves a residual blood of 170 cc. which is probably more than can be accounted for in the auricles. Cournand[9] has observed that a premature beat may eject blood even though the premature contraction begins when the pressure in the ventricle is still too high for blood to have flowed in from the auricles.

It has been shown[30] that the heart volume in healthy young men may scarcely increase at all with moderate work while heavy work produces, on the average, a 12.7 per cent enlargement. Immediately after exercise the heart volume usually decreases below the control value. It is highly probable therefore that the venopressor mechanism for increasing cardiac output by elongation

of the myocardial fibres only comes into action in severe physical effort while in the earlier stages of work the cardiac output is increased by other mechanisms—nervous and humoral.

When the heart is "decompensated," however, a sustained and considerable rise in venous pressure takes place in exercise which persists after exercise is over.[53] This is in contrast with the slight rise followed immediately afterward by a fall occurring in normal healthy subjects.[63] A raised venous pressure occurs in patients with severe anemia in whom the cardiac output is high at rest.[54] Although this raised venous pressure may be regarded as "compensatory," it must, in fact, be the last resource of the compensating mechanisms, for a further rise in venous pressure in such patients is likely to induce a *fall* in cardiac output[56] together with pulmonary congestion and various signs of heart failure. It is clear then that anemic hearts compensated in this manner are, in fact, on the very brink of failure which may readily be precipitated by slight further increases in venous filling pressure.

Venopressor adjustments are therefore to be regarded as subsidiary mechanisms in health, coming into action only in the later stages of severe muscular effort. They come into action more readily in heart disease but their development is an indication of the imminence of heart failure.

RISE OF VENOUS PRESSURE IN CARDIAC FAILURE

Experimental. Starr and his co-workers[59] have produced severe damage to the right ventricle by burning in dogs without any consequent rise of venous pressure. Roos and Smith[50] showed that it was possible to get some rise in venous pressure by embolization of the coronary arteries with starch granules. Very severe diffuse embolization, however, was necessary and unfortunately no observations on change in cardiac output were made. The venous pressure rises achieved were modest, ranging from 1.5 to 3 cm. of water. Landis and his collaborators[27] have also produced impairment of myocardial capacity for work by ligating coronary arteries and by experimental auricular fibrillation. Neither of these methods leads to a rise in venous pressure at rest. Prinzmetal[42] has also noted the absence of venous congestion as a result of extensive coronary ligation. When animals with these impaired hearts, however, are subjected to exercise, the venous pressure rises. This was in contrast with the fall in venous pressure which occurs normally in exercise.[27] In animals with pericardial tamponade the raised venous pressure was found to fall somewhat in exercise, but this was an inconstant result, and in one example in the paper by Landis et al.[27] the increased arterial pulse pressure suggested that the cardiac output did, in fact, increase during the exercise. Inability to increase cardiac output adequately during exercise is probably an early mechanism inducing a rise in venous pressure. (Fig. 1.)

Clinical. In the introductory section reasons were given for discarding the old view that blood is simply dammed up behind the failing chamber, the most cogent of which was the observation that all the phenomena of heart failure may appear with an output raised above the normal.

Among the explanations offered to account for raised venous pressure in heart failure is an increase in blood volume. There is a considerable body of evidence that the blood volume is increased;[16] and in spite of criticisms concerning the validity of the dye method[41] in the presence of large volumes of oedema fluid into which leakage of the dye may take place, the evidence must be accepted as adequate. It has frequently been observed that some concentration of the blood takes place during recovery from cardiac failure.[69] Landis and his group, however, have shown that an increased blood volume is by itself inadequate to maintain a raised venous pressure in animals in which the circulation is otherwise normal.[27] In the presence of heart failure, however, saline infusion will produce a maintained rise in venous pressure,[47] a finding in contrast with the rapid

restoration of venous pressure toward normal in otherwise healthy subjects. It seems unlikely then that a raised blood volume is an important primary event in raising venous pressure but its secondary development in the presence of a failing heart in response to tissue needs at a higher level of cardiac output.[61] The venopressor reaction may be induced, perhaps, by local metabolic changes of an "asphyxial" character in the venomotor centre.

The manner in which the venous pressure

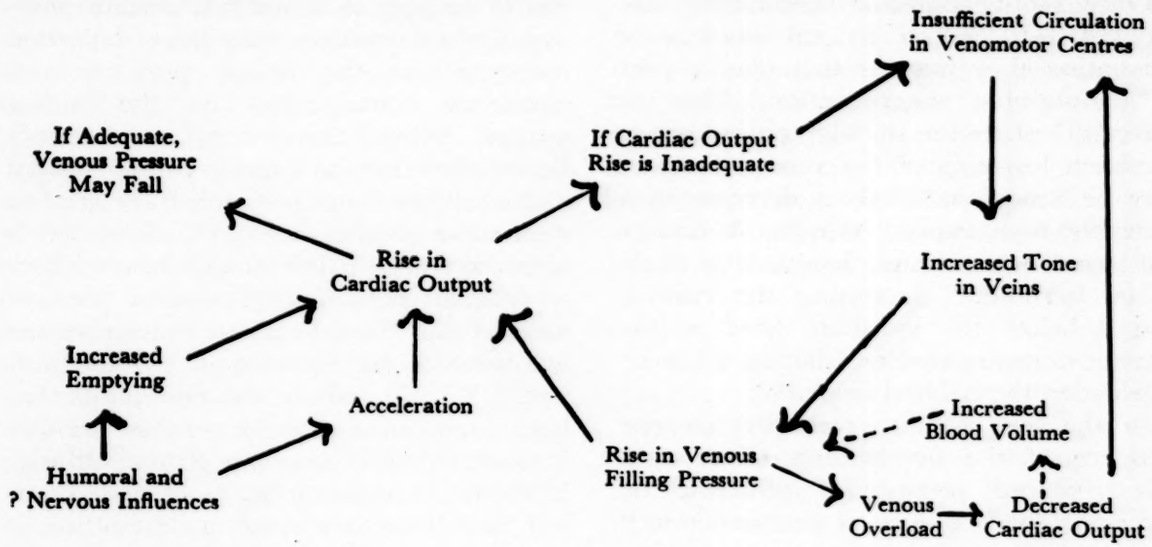

FIG. 1.

may play some part in sustaining venous congestion.

There are numerous instances, however, in which a raised venous pressure may develop so rapidly that increased blood volume cannot be invoked to account for it. An example of this occurs in traumatic pericardial haemorrhage.[66] Here there is probably a reduced blood volume but the venous pressure is raised to a level adequate to maintain filling of the heart against the external pressure exerted by the effused blood. Similarly, there is evidence that the blood volume in some cases of severe anemia is reduced, but in spite of this the venous pressure is often raised.[54] In the absence of a blood volume increase as an initiating mechanism we must postulate the intervention of a venopressor adjustment. In "high output" failure the venopressor mechanism is probably brought into action first rises in failure accompanying valvular hypertensive and ischemic heart disease (low output group) is a matter still somewhat difficult to analyze. Perhaps the clue is to be found in studies of the reaction to exercise. It was found by Schott[53] that exercise was accompanied by a gross and prolonged rise in venous pressure in cardiac patients. This contrasts with normal subjects in whom the venous pressure rises only slightly during the muscular movements, falling below normal immediately the exercise is over.[63] Hickam and Cargill[20] have shown that the cardiac output often fails to rise or may even fall during exercise in cardiac patients when the systemic venous pressure is considerably raised above the pre-exercise level. It would appear, therefore, that a venopressor reaction in response to an inadequate cardiac output during exercise can be regarded as one important

way in which the venous pressure is raised. The well known beneficial value of complete bed rest in the early stages of cardiac failure fits very well with the concept that effort and exercise are important in initiating venous congestion.

Once the venopressor mechanisms are brought into action by an inadequate circulation they may at first play a part in maintaining compensation. This is, perhaps, best seen in the high output group in which lowering of the venous pressure may be accompanied by a decrease in a desirably high cardiac output. A further rise in venous pressure, however, is likely to be harmful,[56] depressing the cardiac output below the optimum level in the manner demonstrated by Starling when he overloaded the isolated heart.[23]

In the low output group the clearest evidence of the overloading effect of a raised venous pressure is obtained by observing the influence of a venesection.[23] In practically every instance simple mechanical reduction of venous pressure so induced leads to an increase in the cardiac output with an increase in the external work of the heart of some 20 to 40 per cent.[23] Conversely, the danger of transfusions in patients with heart failure is well known. In Hickam and Cargill's observations of the fall in cardiac output with the raised venous pressure of exercise it is possible to apply the interpretation that the heart had been subjected to a mechanical venous overload.

This pathologic reversal of the normal relationship between venous filling pressure and cardiac output may bring about a vicious circle in heart failure; the raised pressure tends to keep the output down while the low output will keep the venopressor mechanism in action. (Fig. 1.) In the early stages venesection is beneficial. Patients themselves have found how to induce relief by adopting the upright position, a measure which reduces the pressure in the right auricle, particularly in paroxysmal nocturnal attacks of failure.

INTERPRETATION OF CHANGES IN CARDIAC OUTPUT AND VENOUS PRESSURE IN HEART FAILURE

The importance of venomotor mechanisms adaptable to the circulatory conditions has been emphasized. The possibility has to be kept in mind that certain pharmacologic substances may have important influences on the venous pressure with secondary consequences on the cardiac output. When therapeutic measures in heart failure lead to a rise in cardiac output and a fall in venous pressure, there are two alternative explanations: (1) Evidence is abundant that in low output heart failure a primary reduction of venous pressure such as that brought about by venesection will lead to an increase in cardiac output.[23,46,62] (2) When the circulation has been inadequate and the venous pressure is raised in consequence, a primary change in the heart itself leading to increased output may have as a result a diminution of venomotor tone and a fall in venous pressure. The interpretation of the mode of action of certain drugs used in treatment remains a matter of some difficulty in consequence of these two alternatives.

It has been shown that mersalyl reduces the venous pressure and raises the cardiac output during mercurial diuresis.[34,43] There is no pharmacologic evidence to suggest that mercurials have a primary action on cardiac contractility and the most reasonable interpretation is therefore a venesection-like action resulting from blood volume reduction at the peak of the diuresis.

Theophylline also lowers the venous pressure within a few minutes of injection and this is accompanied by a very considerable rise in cardiac output[21] particularly in hypertensive cardiac failure. The rise in output has been found to be considerably greater than would be expected from simple mechanical reduction of venous pressure, and this action is therefore interpreted as being mainly the result of an adrenaline-like stimulation of cardiac contraction.

The actions of the digitalis series have been much more difficult to interpret on the evidence obtained from clinical experiment.[3,23,36,60] Venous pressure and cardiac output effects are quantitatively similar after digoxin and venesection.[23] There is a considerable consensus that digitalis has a slight but consistent primary venous pressure lowering action in normal animals and man,[5,10,24,52,70] and this action has been regarded as responsible for the fall in cardiac output which takes place when digitalis is given to normal animals and man.[36] From what has already been said about venesection such a venous pressure reducing action might well play a part in producing the cardiac output improvement which follows the administration of digitalis to many patients with low output heart failure.

Further work with ouabain,[3,34] however, shows that the stimulating action of this glycoside on cardiac contractility in the failing human heart is very striking, and in many instances a rise in output precedes significant venous pressure reduction. A similar stimulating action of digoxin, though presumably present, has been much more difficult to demonstrate by clinical experiment. There are many instances in which digoxin appears to have brought about a fall in venous pressure with no significant change or even with a reduction in cardiac output.[22,60] It cannot, therefore, be claimed that the venous pressure falls as a simple secondary consequence of an increasing cardiac output. Quite a small initial fall in venous pressure induced by digoxin in favourable circumstances may induce a cardiac output rise and break the vicious circle of cardiac failure. It is difficult to escape the conclusion that there are two separate actions of the digitalis series which influence cardiac contractility: one is the stimulating action seen in certain types of failing myocardium and which is particularly well seen with ouabain; the other is a venous pressure reducing action, more strikingly seen with digoxin than with ouabain.

There are instances in which both venous pressure and cardiac output seem to be completely refractory to the cardiac glycosides.[68] The significance of this group is not at all clear. It includes instances of anemic heart failure and cases in which the venous pressure has been artificially raised by salt and D.C.A. Wood[68] suggests that these cases may not be in true heart failure, but similar refractoriness may be seen in advanced heart failure and in aortic valve disease particularly. Sometimes the venous pressure reducing action of digitalis may be apparently offset by a pronounced effect of the drug in raising the arterial pressure.[70]

LEFT HEART FAILURE

When the left ventricle fails primarily, a stage may be seen in which venous engorgement affects the pulmonary vessels only while the systemic venous pressure may not be raised outside normal limits. In this state of affairs it seems probable that pulmonary venous engorgement is brought about by an initial lack of balance between right and left heart output. The imbalance can continue only until the pulmonary veins are sufficiently engorged and the pressure within them becomes high enough to drive the left heart to put out a volume of blood equal to that of the right. Pulmonary engorgement is a necessary accompaniment and leads in the first instance to a diminished vital capacity and later to lung oedema. The engorgement of the lung vessels is a major factor in the production of dyspnoea (difficult breathing).[7]

The rise of pulmonary venous and capillary pressure may be responsible for the rise in pulmonary arterial pressure[19] recorded by Bloomfield and others[2] and by Hickam and Cargill[20] in left heart failure. This pulmonary arterial pressure rise is reduced by digoxin[9] and is apparently elevated by ouabain,[3] which is a further interesting point of difference in the action of these two glycosides.

Attacks of acute left ventricular failure are accompanied by further elevation of the arterial pressure, the so-called "Hoch-

druckstauung" of the Germans. Whether this is the cause or consequence of the attacks of failure is not yet clearly defined.

TRICUSPID INCOMPETENCE

The venous pressure change which takes place as a result of relative insufficiency of the tricuspid valves has certain special features. The right ventricle and auricle become functionally a common chamber. During ventricular systole the pressure rises to a high level; this is transmitted into the great veins near the heart with accompanying pulsatile swelling of the liver. It has recently been shown that the pressure beyond the last competent valves in the venous system may be considerably lower than the mean pressure in the central veins.[2,55] This means, in effect, that blood is held up in the peripheral veins during ventricular systole and flows into the central venous pool in intermittent squirts during relaxation of the right ventricle. The last competent valves in the systemic veins proximal to the heart in fact replace the tricuspid valves.

Tricuspid incompetence may occur only in the last stages of heart failure but sometimes it may be present for years in patients who remain ambulant and who may be aware of relatively little breathlessness.

CARDIAC OEDEMA

The relationship of oedema to raised venous pressure remains a perennial problem. Undoubtedly hydrostatic factors are important in increasing the rate of filtration from the capillaries but it seems impossible to account for oedema on this factor alone. There is no relationship between the severity of oedema and the rise in venous pressure.[1] Gross rises of venous pressure have been produced in recent years by various operations designed to limit the spread of venous thrombosis and consequent embolism. Ray and Burch[44] have studied such cases following ligature of the iliac veins and the vena cava. Although the pressure in the veins of the legs was often enormously increased and sometimes there was considerable accompanying oedema, it was observed that the venous pressure often remained considerably raised in the veins of the foot at a time when oedema was disappearing.

A recent attempt to explain some of the discrepancies has been made by Merrill.[38] It was found that the kidney blood flow was grossly reduced in heart failure; as a result of this there was a diminished volume of glomerular filtrate and a very considerable reabsorption of water and salt occurred in the normally functioning tubules. This led to a slowly accumulating salt retention and consequent increase in the water and salt content of the body with developing oedema.

Of the increased retention of salt in heart failure there can be no doubt, but whether it is entirely accounted for by primary reduction in renal blood flow and glomerular filtration rate, as suggested by Mokotoff and his colleagues,[39] is a matter of doubt. Similar reductions of cardiac output and renal blood flow are seen in patients with myxoedema[8] in the absence of symptoms and signs of congestive failure. Similarly the hypothesis of diminished renal blood flow is somewhat strained when patients with so-called "high output heart failure" are considered. In severe anemia the renal plasma flow is normal although the blood flow may be slightly reduced. In other instances it is thought by Stead and his school[60] that the renal blood flow may become inadequate during daily work although it may be nearly normal at rest. These ingenious explanations may account for some of the discrepancies but a great deal more work is needed before we can reach a final assessment of the role of salt retention.

Other factors to be considered in cardiac oedema besides raised venous pressure and salt retention include:

Tissue Tension. When a normal individual stands upright, a certain amount of swelling of the lower limbs will occur, but this swelling does not exceed certain physiologic limits. These limits are imposed by tissue capacity and resistance to further

swelling. For cardiac oedema to develop something has to happen in the subcutaneous tissues to make them accommodate large quantities of fluid. What the process is is not yet clear. It may be partly accounted for by the tissue wasting which occurs in heart failure. Most oedematous patients show considerable loss of tissue, easily visible above the swollen parts of the body.

Diminution of Colloid Osmotic Pressure. The concentration of proteins in the plasma is often somewhat reduced and this no doubt contributes to the ease of filtration of fluid through the capillary walls.

Increased Extravascular Accumulation of Metabolites. In healthy man during exercise the increased formation of chemical products of low molecular weight in the active tissues tends to draw fluid from the blood stream. A similar process may play a part when the cardiac patient tries to take exercise, and furthermore a final equilibrium may not be so quickly established owing to the sluggish circulation.

Increased Permeability of Capillaries. This theory has often been invoked to explain cardiac oedema. Most of the old experiments on which this hypothesis was based involved the effect of total deprivation of oxygen on the capillary walls.[26] We now know that circulating blood in heart failure often returns to the right heart nearly half saturated with oxygen even in the late stages of heart failure. It would be difficult, therefore, to support the hypothesis that oxygen lack plays any importar+ part in the production of increased capillary permeability. The protein content of oedema fluid does not suggest excessive permeability to protein.[65] Smirk[58] thinks that water and salts may pass through the capillary wall more easily and more quickly in congestive failure.

SOME OTHER CONSEQUENCES OF VENOUS CONGESTION

The liver often becomes swollen and the terminal picture of engorgement with disappearance of liver cells in the centres of the lobules is well known. It is doubtful, however, if the degeneration of liver cells is, in fact, a consequence of pressure effects. It is more likely, as Bolton[4] pointed out many years ago, to be the result of diminished blood flow through the liver. Jaundice is frequently present to a slight degree (serum bilirubin 1 to 2 mg. per 100 cc.) in the last stages. Sometimes it may become severe and the mechanism of this jaundice is still a matter of some perplexity. It has been thought that it results from the breakdown of red cells in infarcts in the lungs but there are many instances in which lung infarcts are present with no very significant degree of jaundice and conversely. Poor function of the liver may be suspected as a result of the diminished blood flow. A third factor which may be important is excessively high intravascular pressure within the liver itself which may interfere with the escape of bile from the channels between the liver cells.[57] It is highly probable that various factors are combined and that no single explanation is adequate. In advanced cases of long continued liver congestion a form of cardiac cirrhosis may develop. Often at this stage the jaundice is mild or slight but persistent ascites may become part of the picture. This is a well known phenomenon in constrictive pericarditis in which the occurrence of oedema and ascites is out of proportion to the dyspnoea.

The kidney in addition to circulatory disturbances already described becomes grossly congested. Leakage of albumin then occurs into the urine, often with the appearance of red cells as well.

CONCLUSION

A mechanism by which the venous pressure may be raised in heart failure is summarized in the diagram, and the evidence supporting this conception has been summarized. The writer realizes that there are still numerous perplexing difficulties surrounding the whole problem. He has thought it better, however, to define what seems to be a reasonable line of thought in keeping with the majority of established

facts rather than to overload the argument with conflicting and confusing ideas. In some cases the interpretations may be purely personal but in most instances the observations on which they are based have been substantiated by clinical experience and experiment. The writer expresses the deepest gratitude to all his collaborators and to many fellow workers in the same field in different parts of the world who, by continuous generous interchange of ideas, have helped to mould these opinions.

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ABSTRACTS OF PAPERS PRESENTED AT THE MIDWESTERN SECTIONAL MEETING
HELD IN CHICAGO, THURSDAY, OCTOBER 28, 1948

GASTRIC SECRETORY RESPONSE TO INTRAVENOUSLY ADMINISTERED AMINO ACID MIXTURES.

Paul R. Sharick, M.D. (*by invitation*) and *Darrell A. Campbell, M.D.*, *Eloise, Michigan.*

Individual amino acids given intravenously produce hypoglycemia and a marked acid response due to a mechanism involving the vagus nerves. The humoral-neural mechanism of gastric stimulation due to intravenous amino acids was confirmed in dogs whose non-vagal pouches were proven by use of the insulin test.

Twelve patients were given rapid intravenous infusions of amino acid mixtures, six receiving a commercial enzymatic protein hydrolysate and six a commercial solution of the ten essential amino acids with added glycine. Eight patients had an active peptic ulcer and four patients were without gastric disease. In all patients administration of amino acid mixtures increased free and total gastric acidity. The acid response was variable and approached that following insulin hypoglycemia in only a few cases. In one case the response was abolished by subsequent vagotomy for peptic ulcer. Regurgitation of bile occurred in all cases.

No significant difference was found with the two amino acid preparations used. No correlation was found between blood amino acid nitrogen levels and gastric acid stimulation. In seven instances a moderate volume secretory response was obtained. An initial transitory increase in blood sugar occurred.

Amino acid mixtures are currently being used in the treatment of peptic ulcer. It is suggested that this plan of therapy may be contraindicated due to the gastric acid response. The hypermotility and acid stimulation produced by intravenously administered amino acids calls for caution in their use following gastrointestinal surgery. The concurrent administration of oral antacids may be advisable in such patients.

USE OF THE ALBUMIN FRACTION IN THE ECLAMPTOGENIC TOXEMIAS.

Allen C. Barnes M.D. and (*by invitation*) *Fred B. Hapke, M.D., Columbus, O.* (From the Department of Gynecology-Obstetrics, Ohio State University Medical School.)

In normal pregnancy there is a drop in the serum albumin level with a shift of the A/G ratio; in the pre-eclamptic and eclamptic toxemias of pregnancy these changes in albumin are accentuated, with the A/G ratio approaching 1.

The clinical response to albumin replacement has been reported in the toxemias of pregnancy. The present study is concerned entirely with the fate of such injected albumin in the eclamptogenic toxemias and the effect this treatment has on the patient's protein status. Thirty patients were placed on a diet low in salt and high in protein and were given oral ammonium chloride and high fluid intake. After the patient's condition had stabilized on this regimen (at least three days) the albumin fraction was administered. Changes in total proteins, A/G ratio, plasma volume, electrophoretic picture, hematocrit, urinary volume and albuminuria, as well as changes in blood pressure, weight and symptomatology were noted.

Results to date indicate that the injection of albumin fraction causes a temporary rise in total serum protein levels. During the next forty-eight hours the blood levels drop and there is an increase of albumin loss in the urine, indicating that much of the injected albumin is lost through the kidneys. This increase in albumin excretion is accompanied by a moderate diuresis, and the clinical observations seemed to accompany this temporary increase in urinary output. The alterations in the patient's serum proteins were all temporary; there was no change in blood pressure and no significant evidence of clinical improvement.

This study indicates that elevation of the serum albumin level in patients with the ec-

lamptogenic toxemias is not a specific in the management of the condition.

MERCURY EXCRETION FOLLOWING ORAL MERCURIAL DIURETICS IN MAN. *E. R. Huffman, M.D.* (*introduced by Charley J. Smyth, M.D.*), *Eloise, Michigan.*

Information concerning the route and rate of elimination of mercury following the ingestion of oral mercurial diuretics is limited. Eighteen hospitalized cardiac patients in congestive failure received oral mercuhydrin for four or more consecutive four-day periods, and the excretion of mercury in the stools and urine was determined for periods up to sixteen days following the last dose. The oral diuretic was administered in two forms, a slowly dissolving enteric coating, and in combination with cevitamic acid and coated with a rapidly dissolving sugar coating. The mercury content of the urine and feces was determined by the dithizone method.

When one tablet per day of the slowly dissolving drug containing 39 mg. per tablet was given, the urinary excretion of mercury for the four days of treatment ranged from 2.52 mg. (1.5 per cent) to 4.99 mg. (3.2 per cent); the elimination of mercury in the feces ranged from 98.96 mg. (63.0 per cent) to 152.50 mg. (97.8 per cent). When five tablets were given per day, the urinary excretion of mercury ranged from 1.98 mg. (0.27 per cent) to 20.35 mg. (2.7 per cent) and the fecal mercury ranged from 190.44 mg. (24.5 per cent) to 640.0 mg. (82.0 per cent). When the larger doses of mercury were given, the average daily excretion of mercury in the urine was only 2.41 mg. When five tablets per day of the rapidly dissolving mercury complex containing 19.5 mg. of mercury per tablet were given, the urinary excretion of mercury during the four days of treatment ranged from 0.8 mg. (0.2 per cent) to 8.8 mg. (2.3 per cent). The elimination of mercury in the feces during this same interval ranged from 90.7 mg. (23.3 per cent) to 240.0 mg. (61.5 per cent).

Follow-up studies of mercury excretion indicate a significant delayed excretion of mercury lasting up to sixteen days following the last dose. These data show that with oral administration of mercurial diuretics there is an accumulation of mercury in the body which is slowly excreted. Only minimal quantities of mercury appear in the urine.

RENAL HEMODYNAMICS IN HEART DISEASE. *B. I. Heller, M.D.* and (*by invitation*) *W. E. Jacobson, M.D., Minneapolis, Minnesota.* (From the Department of Medicine, Veterans Hospital and the University of Minnesota Hospitals.)

Renal hemodynamic studies were performed by use of the para-amino hippurate and mannitol clearance methods in thirty-eight male patients with organic heart disease. Patients with hypertension were excluded. The patients were divided into the following three groups: group A, thirteen patients with rheumatic valvular heart disease without previous or present evidence of heart failure; group B, twelve patients admitted with cardiac decompensation but clinically compensated at the time of study; group C, thirteen patients with cardiac decompensation.

In all phases of heart disease there was a disproportionate reduction in the effective renal plasma flow and glomerular filtration rate. This change was most marked in patients with congestive heart failure, and the resultant increase in the filtration fraction indicates a high degree of efferent arteriolar spasm. The cause of this vasospasm is unknown.

It has been generally conceded that tubular function is normal in congestive heart failure. Therefore, the reduction of maximal tubular excretory capacity in group C patients was of great interest. It appears most likely that tubular ischemia accounts for this reduction.

EFFECTS OF MORPHINE ON RENAL CLEARANCES OF PARA-AMINO HIPPURATE AND SODIUM THIOSULFATE IN THE HUMAN KIDNEY. *Willis E. Brown, M.D., Robert Hodges, M.D.* and *J. T. Bradbury, Sc.D., Iowa City, Iowa.* (From the Department of Obstetrics and Gynecology, University of Iowa College of Medicine.)

Morphine antidiuresis has been previously reported by us. The mechanism of this reduction seems to be independent of sedation, hypnosis, induced sleep or postpituitary hormone release.

Using the renal clearances of para-amino hippurate and thiosulfate as a measure of renal plasma flow and glomerular filtration, respectively, we have found that morphine given intravenously in doses of 16 mg. produced the

following effects: (1) a consistent and significant lowering of urine flow; (2) a reduction in the renal plasma flow; (3) no significant change in glomerular filtration; (4) a slight rise in filtration fraction; (5) an increased re-absorption fraction resulting in decreased urine output.

We believe that the antidiuretic effect of morphine is largely due to this increase in the re-absorption fraction.

These observations showing decreased clearance of para-amino hippurate (a cortical function) and increased tubular re-absorption of water (a medullary function) are compatible with the vascular shunt theory of Truetta.

ADMINISTRATION OF TETRAETHYLAMMONIUM BROMIDE BY SLOW CONTINUOUS INTRAVENOUS INFUSION. *C. W. Ulrich (by invitation), J. D. Peirce, Jr., M.D.* and *K. G. Kohlstaedt, M.D., Indianapolis, Indiana.*

Since the effect of a single intravenous injection of TEAB is brief and is often accompanied by a marked decline in blood pressure, the safety and practicability of a continuous intravenous infusion of the drug was investigated. With TEAB entering the vein at the rate of 6 to 10 mg. per minute, a definite rise in skin temperature could be maintained for six to eight hours in normotensive and in hypertensive persons. Arterial pressure was reduced very little or not at all. Side effects did not occur until the infusion rate exceeded 7 mg. per minute and when more than 12 mg. per minute were given; all subjects exhibited mild untoward symptoms. The maximum amount of TEAB administered was 16 mg. per minute. In normotensive persons at this rate of infusion a mean rise of 5°C. was produced in the skin temperature over the great toe. In patients with thrombo-angiitis obliterans or with obliterative arteriosclerosis the continuous infusion of 6 to 13 mg. of TEAB per minute gave moderate to complete relief from pain and the mean rise in skin temperature was never more than 3°C. This method of administration was also used to control intractable diarrhea in two persons with ulcerative colitis. If the rate of infusion is accurately controlled by a Harvard tunnel clamp, intravenous administration of TEAB can be maintained for at least eight hours, with few if any unpleasant reactions.

MINIMAL SODIUM DIET; A CONTROLLED STUDY OF ITS EFFECT UPON THE BLOOD PRESSURE OF AMBULATORY HYPERTENSIVE SUBJECTS. *Milton Landowne, M.D. (by invitation) Walter Thompson, Jr., M.D.* and *(by invitation) Barbara Ruby, B.S., Chicago, Illinois.*

Administration of a diet rigidly restricted in sodium may influence the habits and reactions of the patient profoundly, altering blood pressure through mechanisms unrelated to the sodium restriction *per se*. A controlled evaluation of these factors in the non-hospitalized patient is needed. Accordingly, twenty-one hypertensive subjects were placed on an adequate diet containing less than 300 mg. of sodium per day and were followed for approximately eighteen weeks. Weekly blood pressure and twenty-four-hour urine analyses were made. All subjects received medication consisting either of 4 Gm. of NaCl a day or placebos. At six-week intervals the medication was either changed or continued according to pre-arranged schedules established by the pharmacist.

The experiment thus consisted of three periods, differing only in that during one (or two) period(s) supplemental sodium chloride was administered, while in two (or one) period(s) the sodium intake remained at a bare minimum. Neither the investigator nor the subject was aware of the nature of the medication.

Satisfactory data were available from only eight of the subjects. The criteria for their selection required that the twenty-four-hour urinary sodium average below 500 mg. for at least one period and over 1,000 mg. for at least one period. The average systolic and diastolic blood pressure during rigid sodium restriction was 4.96 and 4.72 mm. of Hg lower than during the periods of added sodium, respectively. These data appear to be significant statistically.

In summary, a diet rigidly restricted in sodium is difficult to administer successfully to ambulatory hypertensive subjects. A difference of less than 5 mm. Hg in average blood pressure was observed, ascribable to the effect of NaCl restriction alone.

PROGNOSIS IN UNTREATED ARTERIAL HYPERTENSION: REPORT ON ONE HUNDRED SEVENTEEN PATIENTS UNDER FIFTY-THREE YEARS OF AGE FOLLOWED FOR EIGHT TO TEN YEARS. *Arthur H. Griep, M.D., (by invitation) George R. Barry, M.D.* and

(*by invitation*) *Winston C. Hall, M.D., Ann Arbor, Michigan.* (From the Department of Internal Medicine, University of Michigan Medical School.)

One hundred seventeen patients (forty-four males and seventy-three females) with essential hypertension were followed for eight to ten years. All had been carefully studied initially and were suitable candidates for sympathectomy or medical treatment. Primary renal disease was excluded and the blood pressure was above 160 mm. systolic and 110 mm. diastolic. When possible, the living patients were re-examined and a history, physical examination, electrocardiogram, teleoroentgenogram, urinalysis, urine concentration test, urea clearance and ophthalmologic examination were carried out.

The average age at the start of the interval was 43.7 years for the males and 41.3 for the females. There was a gross mortality rate of 53.8 per cent and a corrected rate of 50.3 per cent. There was a 70 per cent mortality in males as compared with 43 per cent for the females.

Eighty-eight per cent of the patients showed less than 40 mm. systolic and 15 mm. diastolic change in blood pressure. In one case the blood pressure fell to normal levels without known cause. Patients with blood pressures above 200 mm. systolic and 130 mm. diastolic, with decreased functional capacity of the heart, cardiac enlargement, abnormal electrocardiogram, abnormal urinalysis and funduscopic abnormalities, sustained a higher mortality rate. In this group of patients the most common cause of death was cerebrovascular accident (39.6 per cent) and cardiac failure (28.5 per cent).

Of fifty-one patients living 19 per cent are symptom-free at the present time. Sixty-one per cent are mildly symptomatic but can carry on with their daily work. Seventeen per cent are ambulatory but unable to work. One patient is bedridden and the symptoms and working capacity of two patients are unknown.

Observations on the Effect of a High Fluid Intake in Valvular Heart Disease in the Last Trimester of Pregnancy.

W. W. Hurst, M.D. (by invitation), F. L. McPhail, M.D. and F. R. Schemm, M.D., Great Falls, Montana.

Observations were made during twenty-two periods in eighteen pregnancies of seventeen patients with severe rheumatic heart disease. All had classical signs of mitral stenosis, six with aortic insufficiency and two with subacute bacterial endocarditis. All exhibited signs of myocardial failure other than edema of the lower extremities before therapy was begun, while one had profuse pulmonary edema, one permanent auricular fibrillation and 6 transient fibrillation. Two of the eighteen pregnancies were terminated by cesarean sections; labor was spontaneous in seven and induced in nine.

The average length of the twenty-two periods was twelve days, the maximum thirty days; the average daily intake was 3,000 cc. or over in nineteen periods, more than 4,000 cc. daily in eight and from 5,000 to 6,000 cc. in four of the periods. In nine of the twenty-two periods intravenous fluids were given to supplement oral intake, in amounts of from 500 to 3,000 cc. in twenty-four hours. In two instances 16,000 and 14,500 cc. of fluid were given by vein in two eight-day periods. Isotonic dextrose in distilled water was used except when emesis or duodenal drainage called for sodium chloride replacement.

The combination of marked mitral stenosis and near-term pregnancy should put the heart at a maximum mechanical disadvantage. Yet there was no evidence that the rather large amounts of plain water given, in these twenty-two observations to maintain an adequate water balance, either hindered the clearing of heart failure or embarrassed the circulation.

Unipolar Electrocardiographic Study of Left Ventricular Hypertrophy. The Electrocardiogram with Left Axis Deviation.

Ernest Goulder, M.D. and (*by invitation*) *Wright Adams, M.D., Chicago, Illinois.*

This study presents ninety-four selected cases in which the electrocardiogram was characterized by left axis deviation with an rS type of QRS in lead III and in which the six multiple precordial leads of Wilson (V leads) and the three augmented extremity leads of Goldberger (AV leads) were used to supplement the three standard leads.

A survey of the group as a whole permitted classification of all tracings into four major categories on the basis of two fundamental criteria in lead aVL: (1) An R wave 9 mm. or

more in amplitude and (2) a ratio, expressed in per cent, of the amplitude of T to the amplitude of R that was less than 10 per cent (T/R ratio).

The first group was characterized in lead aVL by an R wave less than 9 mm. and by a T/R ratio greater than 10 per cent and was also associated with normal standard and unipolar leads. Clinically, this group was not correlated with left ventricular hypertrophy. The second group was characterized in lead aVL by an R wave greater than 9 mm. in amplitude and by a negative T/R radio due to an inverted T wave. Most of the patients in this group presented in the standard leads the left ventricular strain pattern of Barnes and Whitten. All showed an excellent correlation with disease processes known to be associated with this pattern. The third group was characterized in lead aVL by an R wave in excess of 9 mm. and by a T/R ratio less than 10 per cent due to a relatively low upright T wave. Many of these tracings were associated with a left ventricular hypertrophy pattern in the standard leads in which a low T-I was associated with an upright T-III, but in others the abnormality of the T waves in the standard leads was less readily expressed. This group showed a good correlation clinically with disease processes associated with left ventricular hypertrophy. The fourth group was characterized in lead aVL either by an R wave greater than 9 mm. or by a T/R ratio less than 10 per cent and clinically had a poorer correlation with left ventricular hypertrophy.

The utilization of these two criteria in lead aVL appears to be a useful adjunct in the electrocardiographic evaluation of left ventricular hypertrophy.

EFFECT OF POSITION ON THE Q-T COMPLEX IN THE WOLFF-PARKINSON-WHITE SYNDROME AND BUNDLE BRANCH BLOCK. *Saul L. Silver, M.D. (by invitation) Simon Zivin, M.D. (by invitation)*, and *Theodore R. Van Dellen, M.D., Chicago, Illinois.*

Eighteen cases of Wolff-Parkinson-White syndrome were collected and the patients' electrocardiograms compared with the typical bundle branch block. Lead I was taken in all patients in the reclining left and right lateral positions. Similar changes occurred when the position was changed in those with Wolff-Parkinson-White syndrome and in the eight patients with bundle branch block. These similarities suggest that the two conditions are related and lend evidence to the observation that Wolff-Parkinson-White syndrome is not entirely benign.

COMPLEMENT-FIXATION STUDIES WITH YEAST-PHASE ANTIGEN IN EXPERIMENTAL HISTOPLASMOSIS. *Chris J. D. Zarafonetis, M.D., Ann Arbor, Michigan.*

Diagnosis of histoplasmosis can be made with certainty only by the isolation and identification of the causative fungus, Histoplasma capsulatum. Since material suitable for culture is not always readily accessible, other diagnostic aids have been sought. A skin test for histoplasmosis was introduced in 1941 but has been found to have little or no clinical value. The purpose of this report is to present preliminary observations on another possible diagnostic aid, namely, the complement-fixation test.

The antigens employed in this study consisted of suspensions of yeast-phase organisms grown on sealed blood-agar slants or in liquid Dubos media containing albumin. The organisms were killed, harvested and repeatedly washed by centrifugation and resuspension in physiologic saline solution containing 0.1 per cent formalin.

Groups of rabbits and guinea pigs were inoculated with suspensions of living yeast-phase organisms. Antisera were obtained by periodic bleeding of the animals and selected sera were used for the titration of antigens. The test used employs serial two-fold serum dilutions, two antigen units and two full units of complement. After overnight refrigeration the hemolytic system is added. This consists of equal parts of a 3 per cent suspension of sheep erythrocytes and amboceptor diluted to contain three hemolytic units. After one-half hour at 37°C. the test is read in the customary manner.

Tests were performed on sera from the inoculated animals and a progressive rise in antibody titer was detected in every instance. Assuming that the antigen is specific, this is considered a diagnostic response. Sera from humans hospitalized for various disorders were also tested. A surprising number of such sera fixed complement in low dilution. Before the test may be utilized for clinical or epidemiologic studies, however, its specificity must be demonstrated through additional studies.

EXPERIENCE WITH DARVISUL (PHENOSULFAZOLE) IN THE TREATMENT OF CLINICAL AND EXPERIMENTAL POLIOMYELITIS. *Morris Schaeffer, M.D.* and *(by invitation) John A. Toomey, M.D., Cleveland, Ohio.* (From the Department of Pediatrics, Western Reserve University and Contagious Department of City Hospital.)

A new sulfonamide compound, phenosulfazole, said to be therapeutically beneficial in poliomyelitis was administered parenterally and orally to sixty-eight patients at the onset of the acute phase of poliomyelitis. The outcome in these patients was compared with sixty-nine untreated control patients selected alternately on admission. No evidence was obtained that the natural course of the disease was affected by this treatment.

Similarly, in the experimental disease produced in 150 mice with the Lansing strain of poliomyelitis virus, administration of phenosulfazole prior to or simultaneously with infection failed to prevent paralysis or death in the treated animals.

PRELIMINARY REPORT ON THE PULMONARY CIRCULATION IN BRONCHIAL ASTHMA. *H. A. Zimmermann, M.D., Cleveland, Ohio.*

A series of five patients with typical attacks of bronchial asthma was studied by means of intracardiac catheterization of the pulmonary artery by the method of Cournand. Pulmonary arterial pressures, femoral or brachial arterial pressures, the electrocardiogram and phase of respiration with a superimposed time trace were recorded simultaneously. This was done by means of pressure transmitters, strain gages, strain amplifiers and a six-channel, direct-writing Brush oscillograph. Cardiac outputs were determined by the Fick principle using the Scholander method for blood oxygen levels and the Rahn method using a Pauling oxygen analyzer for determination of the amount of oxygen in the expired air.

All patients had a moderate to severe attack of bronchial asthma and all had abnormally high pressures in the pulmonary artery. One patient had a few wheezes in the chest with normal pulmonary arterial pressure, but after an injection of mecholyl a moderately severe attack of asthma was induced and the pulmonary arterial pressure was elevated above normal.

Aminophylline may relieve an acute attack of bronchial asthma and the pulmonary arterial pressure drops to a subnormal level. Adrenalin, on the other hand, may relieve an acute attack of bronchial asthma but it causes a distinct elevation in the pulmonary arterial pressure. In patients whose asthmatic attacks were relieved we have found that the cardiac output was higher following the use of adrenalin than following aminophylline.

FIBRINOLYSIS AND PROTHROMBIN IN EXPERIMENTAL APPENDICEAL PERITONITIS. *Carlos Tanturi, M.D., Raymond Anderson, M.D.* and *Nicholas Wetzel, M.D., (introduced by Walter J. Maddock, M.D.), Chicago, Illinois.* (From the Department of Surgery, Northwestern University Medical School.)

Appendiceal peritonitis was produced in forty-six dogs using the technic of Bowes. Serum fibrinolytic activity was studied pre- and postoperatively using the method of Kay and Lockwood. Variations in blood prothrombin were measured by the technic of Tanturi and Banfi.

Results showed that a decrease in prothrombin is observed in appendiceal peritonitis in 85.7 per cent of the dogs, indicating some degree of injury to the liver. Forty-six per cent of the dogs showed fibrinolytic activity in the serum during the postoperative period. A decrease in prothrombin bears a closer relationship to death than does any variation in the fibrinolytic-antifibrinolytic equilibrium. An early postoperative decrease in prothrombin corresponded with a higher incidence of death. Chloroform anesthesia was given in ten dogs to increase liver damage. These dogs died earlier than those dogs who received no chloroform although no increase in fibrinolysis or hypoprothrombinemia was observed.

The decrease in prothrombin is not the cause of death but appears to be the reflection of the primary cause of death in the animal more than the fibrinolytic activity of the blood.

ESTIMATION OF MEGAKARYOCYTE CONTENT OF ASPIRATED STERNAL MARROW. *Lawrence Berman, M.D. (by invitation), Arnold R. Axelrod, M.D. (by invitation) Else S. Kumke, B.S., Detroit, Michigan.* (From the Departments of Pathology and Medicine,

Wayne University College of Medicine, and the City of Detroit Receiving Hospital.)

The present methods of estimating the megakaryocyte content of aspirated sternal bone marrow are not satisfactory. Methods based on examination of marrow smears are unsatisfactory because the aspirated marrow is unavoidably diluted with sinusoidal blood; the distribution of megakaryocytes on smears is irregular; the total nucleated cell content of bone marrow is variable from patient to patient and the incidence of megakaryocytes may vary independently of the incidence of other nucleated cells. Hemocytometer counts of megakaryocytes are subject to error introduced by variable dilution with sinusoidal blood and also by the variable base of total nucleated cells.

The present study showed that neither the smear nor chamber count method yields results which correlate with those obtained by study of actual marrow tissue sections. Instances of low counts obtained by the smear or chamber methods in patients with high megakaryocyte content, as revealed in marrow sections, were encountered. Even the section count produces arbitrary values which cannot be converted into terms expressive of the actual number of megakaryocytes per unit volume of marrow. Hence all section counts obtained from patients must be compared with counts made by identical means from suitable controls.

Since the error of underestimating the megakaryocyte content of aspirated marrow samples may be of clinical importance, especially when the question of splenectomy for thrombocytopenic purpura is presented, examination of marrow sections for megakaryocytes should not be omitted whenever the chamber or smear methods yield values suggestive of decreased megakaryocytogenesis.

CLINICAL EVALUATION OF TETRAETHYLAMMONIUM CHLORIDE IN CORONARY HEART DISEASE. *Harold W. Christy, M.D., (introduced by Howard A. Lindberg, M.D.), Chicago, Illinois.*

Ten patients presenting symptoms that were considered classical of chronic coronary insufficiency with the anginal syndrome, most of whom had abnormal electrocardiograms, were treated with bi-weekly intramuscular injections of tetraethylammonium chloride. The dosage ranged from 200 to 800 mg. per injection. No reactions of moment were encountered in this group. Some of the patients received injections over a period of at least a year. Two patients had complete disappearance of their anginal syndrome with improvement in the electrocardiogram during the course of treatment. Five patients reported considerable improvement in their symptoms. None developed what might be considered anginal equivalents. Two had improvement in their electrocardiograms. Two patients reported no improvement whatsoever and one of them was the only one that did not have electrocardiographic or physical findings to support a diagnosis of coronary insufficiency. The tenth patient did not report for continuation of therapy and the results of treatment in this case are not known.

CAUSES OF DEATH IN ANEURYSMS OF THE HEART. *Wendell A. Shullenberger, M.D., Indianapolis, Indiana.* (From the Division of Internal Medicine, Methodist Hospital.)

It is frequently stated that cardiac aneurysm is not incompatible with a considerable degree of physical activity and it is a fact that despite their spectacular pathologic features these aneurysms when fully healed and fibrosed undergo rupture infrequently. The usual causes of death following establishment of this condition in the heart are congestive failure, rupture and "sudden death." The last group deserves more attention than it has received. The case reported here is believed to be unusual in the nature of the terminal event.

A diagnosis of acute coronary thrombosis was made in a fifty year old male after he had suffered three attacks of epigastric pain in a period of eleven days. Aneurysm of the left ventricle was diagnosed by roentgenogram after three weeks in the hospital. He became ambulatory and carried on fairly normal business activities for thirteen months but died suddenly after several attacks of epigastric pain. Autopsy showed a large aneurysm of the left ventricle and a fresh thrombosis of the circumflex branch of the right coronary artery.

Statistics obtained from analysis of forty-six well studied cases selected from the literature show that somewhat less than 50 per cent of patients may be expected to survive from a few months to several years. It is further shown that

when aneurysm of the heart has been established, 46 per cent died of congestive failure, 11.5 per cent of rupture of the aneurysm, 11.5 per cent of acute coronary thrombosis, 8 per cent of left ventricular failure and 8 per cent of other causes. The remaining 15 per cent are classified as "sudden deaths."

AN ENDOCRINE FINDING APPARENTLY CHARACTERISTIC OF GOUT. VERY LOW URINARY 17-KETOSTEROID EXCRETION, WITH CLINICALLY NORMAL ANDROGENIC FUNCTION. *W. Q. Wolfson, M.D., R. Levine, M.D., H. S. Guterman, M.D., C. Cohn, M.D., H. D. Hunt, M.D.* and *E. F. Rosenberg, M.D., Chicago, Illinois.* (From the Department of Biochemistry and the Department of Metabolic and Endocrine Research, Medical Research Institute, Michael Reese Hospital; the Arthritis Clinic and the Division of Medicine, Michael Reese Hospital, Chicago; and the Department of Internal Medicine, Albany Medical College, Albany, N. Y.)

The urinary 17-ketosteroids (KS) are the chief identified urinary excretory products of male sex hormone metabolism. Urinary KS values depend upon both testicular and adrenal androgen production in men and upon adrenal androgen production in women.

Decreased urinary KS output has been found in all of a group of eleven gout patients (average 3.0 mg./day). Decreased excretion occurred in all phases of the disease including asymptomatic gout. Similar decreases did not occur in patients with idiopathic hyperuricemia and in males with rheumatoid polyarthritis or spondylitis.

Review of currently available endocrine explanations for decreased 17-ketosteroid output of the degree noted indicated none to be acceptable. Injected testosterone was recovered as urinary 17-ketosteroid to the usual extent and no defects in hepatic function were noted. Renal function was well enough preserved to make "retention" of 17-ketosteroids improbable. In spite of accumulating evidence that altered adrenocortical glycocorticoid production may be important in acute gouty attacks there was no evidence of "resistance stage" endocrine status at other periods.

Biologic evidence of androgen activity was normal in nine of the ten men in this group. A review of a much larger series of patients gave additional evidence that hypogonadism is not clinically prominent in patients with gout.

The findings of very low outputs of urinary 17-ketosteroids in the presence of normal biologic androgen activity appears to be a new endocrine finding which is characteristic for gout. Our working hypothesis is that in gout biologic androgen activity is maintained by an androgenic hormone which does not make an important contribution to urinary 17-ketosteroids when metabolized.

COMPARATIVE SYMPATHETIC BLOCKING AND ADRENOLYTIC ACTION OF FOUR DRUGS IN THE HUMAN SUBJECT. *J. W. Avera, M.D.* (*by invitation*), *S. W. Hoobler, M.D.*, (*by invitation*) *S. G. McClellan, M.D.* and (*by invitation*), *W. J. Little, M.D., Ann Arbor, Michigan.* (From the Department of Internal Medicine, University Hospital.)

Comparative effects of the intravenous injection of tetraethylammonium chloride (TEA), (6 mg./Kg. body weight); priscol, (0.6 mg./Kg. body weight); dihydroergocornine (DHO), (0.005–0.01 mg./Kg. body weight) and piperidomethyl benzodioxane (933F) (10 mg./square meter body surface) on peripheral blood flow were studied by means of venous occlusion plethysmograph. As a result of these studies we have arrived at the following conclusions:

Tetraethylammonium increases peripheral blood flow solely by a sympathetic blocking action. It does not produce vasodilatation in the denervated extremity and it has no adrenolytic effects. When injected intra-arterially, it has a slight vasoconstrictor action in concentrations well above those usually attained by intravenous injection.

Priscol increases blood flow by a direct vasodilator action. It has weak adrenolytic properties when given intravenously and a more marked effect when given intra-arterially. It probably has relatively little sympatholytic action when administered intravenously since the increase in blood flow in the innervated extremity is considerably less than that following paravertebral block or ganglionic blockade with tetraethylammonium and since the innervated and denervated extremity show approximately equal vasodilation following injection of the drug.

The increase in peripheral blood flow after

dihydroergocornine is, for similar reasons, probably not dependent on its sympathetic blocking properties. Since the vasodilator effect after intravenous injection was delayed in onset and since no increase in blood flow occurred on intra-arterial injection, it is possible that the drug undergoes conversion to a vasodilator agent in the body. Dihydroergocornine is not adrenolytic in the usual intravenous dosage but possesses this property when given intra-arterially in high concentration.

In the usual intravenous dosage benzodioxane has no peripheral vasodilator action and is therefore not sympatholytic. Intra-arterially it has no direct vasodilator action and blocks epinephrine vasoconstriction only when injected intra-arterially in high concentrations.

OBSERVATIONS ON AIR SWALLOWING DURING OPERATIONS. *John L. Bell, M.D.* and *Walter C. Maddock, M.D., Chicago, Illinois.*

It is generally accepted that the main source of gas in abdominal distention is external air, and the way it is alleged to enter the alimentary canal is commonly suggested by the term "swallowed air." To learn more about swallowing during operations a series of twenty-three patients were observed.

A Levine tube was passed into the stomach and all gas was removed and measured. Swallowing movements during the induction of the anesthesia varied from 0 to 5. This is in great contrast to earlier work in which open ether was used and it is probably due to our rapid induction. No swallowing movements were observed during the operations.

The amounts of gas aspirated during operations under spinal-pentothal and inhalation anesthesia ranged from 0 to 130 cc., with an average of 73 cc. In one case 780 cc. were aspirated from the stomach during a period in which there was abnormal respiration due to the patient's tongue dropping back. With this obstructed airway, it is believed that air entered the esophagus rather than the trachea.

In five of ten cases in which curare was used to supplement the inhalant anesthetic some intercostal paralysis occurred, necessitating positive pressure to augment respirations. The amounts of gas aspirated in these cases varied from 300 cc. to 1,700 cc. With the exception of the five cases in which curare necessitated positive pressure anesthesia, the total volume of gas aspirated during the operations would probably not contribute to postoperative abdominal distention.

RATIONALE OF THERAPY IN ACUTE VASCULAR OCCLUSIONS BASED ON MICROMETRIC OBSERVATIONS. *Harold Laufman, M.D., Wayne B. Martin, M.D.* and *Stanley W. Tuell, M.D.* (*Introduced by Howard A. Lindbergh, M.D.*), *Chicago, Illinois.* (From the Department of Surgery, Northwestern University Medical School.)

By means of a modified Kniseley fused quartz rod transillumination apparatus, actual micrometric measurements of small vessel caliber made it possible to evaluate the effects of certain therapeutic measures in acute vascular occlusions. All observations were made on mesenteric vessels in the dog. Much of the therapy in vogue today is controversial and there is confusion concerning the physiologic responses to vascular occlusions. It was necessary, therefore, to establish the typical patterns of response in small vessel caliber following occlusions. All occlusions were made using a rubber tipped clamp. Following main stem arterial occlusion, both the small artery and vein under observation diminished in caliber. After release of the occlusion a small artery remained in moderate spasm for a short period of time before returning to the control caliber. This phenomenon we termed residual vasospasm. Following main stem venous occlusion, the small veins became dilated while the small arteries exhibited a marked diminution of caliber. After release of a venous occlusion temporary residual spasm in the small artery was again noted. As the artery returned to its control caliber the engorged vein also regained its control diameter.

Alterations in the basic pattern as produced by certain therapeutic measures were then observed. Experiments with sympathectomized specimens indicate that the afferent and efferent fibers of both arteries and veins are largely responsible for the patterns of response following occlusions while the pressure gradient of blood flow through the vascular tree became important only when the spastic impulses were overcome by the intravascular pressure. Such a situation accounts for venous engorgement during venous occlusion in the presence of increased tonus in the vein wall. Regional sympathetic denervation eradicates the pattern

of small vessel spasm to an extent unequalled by vasodilators employed. Oxygen therapy was found to have no effect on vessel caliber. Papaverine hydrochloride was found to be of value in releasing some of the reflex arterial vasospasm in venous occlusions if used before thrombosis occurred. In arterial occlusions the drug was of value only when collateral arteries existed above the occlusion. Once an occlusion was released the drug was able to eradicate residual spasm in the small vessels. Tetraethylammonium chloride in non-shock-producing doses was able to counteract the vasospastic effects following acute venous occlusion in about 50 per cent of cases while in acute arterial occlusions it was without value unless there were collateral vessels present.

EFFECTIVENESS OF ANTICOAGULANT THERAPY AS OBSERVED IN 300 CASES. *Ivan F. Duff, M.D.* (*Introduced by W. D. Robinson, M.D.*), *Ann Arbor, Michigan.* (From the Department of Internal Medicine, University of Michigan.)

Among those given treatment were 133 patients with peripheral venous thrombosis, thirty-five with pulmonary embolism and twenty-seven with myocardial infarctions; seventy-four postoperative patients were treated prophylactically. One hundred thirteen received preliminary heparinization, the remainder received only dicumarol.

Dicumarol required about 2.7 days to effect therapeutic prothrombin concentrations (30 per cent or less) which were maintained an average of ten days. Excessive hypoprothrombinemia occurred in 17 per cent of the patients. Dicumarol induced bleeding in 11.2 per cent of the subjects; this occurred in three-fifths of those who had prothrombin concentrations below 20 per cent. The incidence of minor and major bleeding was 61 per cent and 29 per cent, respectively; there was one fatality from hemorrhage. Heparin rarely induced bleeding.

One of the postoperative patients receiving prophylactic dicumarol developed thromboembolism at a low level of prothrombin. Satisfactory resolution of venous thromboses resulted in 90 per cent of the patients; this was accelerated by employing preliminary heparinization. In eight of these patients thromboembolism occurred or progressed at effective prothrombin levels.

All the patients (nineteen) with simple postoperative pulmonary embolism recovered. Five deaths occurred in the remaining sixteen patients with pulmonary embolism and infarction, the majority of whom had organic heart disease and had sustained their infarction before hospitalization. Anticoagulants were used with poor success in treating recurrent pulmonary emboli arising from mural thrombi.

Five (18.5 per cent) of the patients with myocardial infarctions died. Mural thrombi, present in two, were associated with recurrent pulmonary infarctions in one subject. Among those who lived secondary thromboembolism occurred in 11.1 per cent.

Case Report

Weber-Christian Disease*

RICHARD J. KENNEDY, M.D. *and* LOUIS R. MURPHY, M.D.
New York, New York *Seattle, Washington*

WEBER-CHRISTIAN disease, or relapsing, febrile, nodular non-suppurative panniculitis, has been regarded as a rare disease but is nevertheless of interest to both the internist and to the pathologist; to the former because of the striking febrile reaction associated with minimal, localized pathologic changes and to the latter because of its histologic resemblance to many "nodular diseases."

TABLE I
DISTRIBUTION OF PATIENTS ACCORDING TO AGE

Age	No. Patients
0– 9	2
10–19	4
20–29	6
30–39	11
40–49	5
50–59	9
60–69	1

The purpose of this paper is first, to review the clinical and pathologic findings in Weber-Christian disease in order to establish criteria for diagnosis; second, to review briefly the cases reported since 1944; third, to add three cases not previously reported and finally, to suggest a relationship between Weber-Christian disease and dermatomyositis.

Weber-Christian disease has been reported in every age group. (Table I.) The youngest patient was a twenty-three-month old male and the oldest a man of sixty-four. In the thirty-eight cases reported from 1892 to the present 71.8 per cent have occurred in females. Since 1944, 50 per cent of the cases have occurred in males.

The disease may be ushered in abruptly or preceded by indefinite prodromas for two to four weeks. The more common prodromal symptoms are general malaise, low grade fever, oropharyngeal infections, vague joint pains or manifest arthritis.

Fever, ranging from 99° to 106.4°F., has been present in 87 per cent of the cases. The rise in temperature is gradual and coincides, as a rule, with the appearance of subcutaneous nodules or fever may not appear until softening of the nodules occurs. The subcutaneous nodules have varied in diameter from 1 to 12 cm. and in numbers from one to thirty. While the hands, face and feet are usually spared, nodules have appeared on all parts of the body and have been especially common on the thighs. (Table II.) In 78 per cent of the cases the nodules were tender but pain was a variable symptom.

TABLE II
SITES INVOLVED IN THIRTY-EIGHT PATIENTS

Sites	No. of Patients
Thigh	28
Leg	25
Arm	24
Trunk	22
Buttock	2
Breast	2
Feet	1
Face	1

The overlying skin may be red if the nodules are superficial. When involution begins, the skin becomes pigmented and atrophy occurs frequently (72 per cent of cases). In a few instances rupture of a nodule occurred without suppuration and a cloudy, yellow, fatty fluid was extruded. With one exception,[1] admittedly due to contamination, smear and culture of such fluid did not reveal bacteria.

Fever persists as long as new nodules appear and until those already present regress. The longest febrile period reported for a single relapse has been 115 days.

* From the Medical Division, St. Vincent's Hospital, New York, N. Y.

Relapses are common and have recurred for as long as fifteen years. In three of the eight cases reported since 1944 splenomegaly has been noted.

Early in the course of the disease leukopenia is the rule with the leukocytes usually less than 7,000/cu. mm. (five of eight cases). The lowest count[2] found was 1,000/cu. mm., with moderate lymphocytosis. Baumgartner and Riva[1] noted that leukocytosis, with an increase in segmented forms, followed the initial leukopenia when involution and softening of the nodules occurred.

Although the clinical picture appears to be fairly constant, the pathologic findings are diverse. Some of the recent cases bear little resemblance to the original pathologic descriptions. Christian[3] described the microscopic appearance of "cellular infiltration of the panniculus adiposus with at times extension into the fat of the adjacent layers. The cells are lymphocytes, plasma cells, a few polymorphonuclear leukocytes, endothelial cells phagocytic for fat droplets and fibroblasts in various admixtures. An occasional multinuclear giant cell is seen. Some areas show a granular appearance due to necrosis of cells and fat tissues." Spain and Foley,[4] Friedman,[5] Allen[6] and Kritzler[7] in their biopsies noted the infiltration to be composed mainly of lymphocytes and large mononuclears. Larkin et al.,[8] Arnold[9] and Zee[10] on the other hand describe infiltration of the areas with polymorphonuclear and mononuclear cells with few lymphocytes present. We believe that the variation in the pathologic findings may be due to the difference in age of the nodules biopsied. Spain and Foley[4] whose patient was autopsied divided the changes in the panniculus into three stages: In the earliest lesions small accumulations of fat-laden macrophages were noted. In larger lesions small central areas of fat necrosis were seen, about which were lymphocytes, polymorphonuclears and fat-laden macrophages. The older lesions showed a decrease in necrotic material and inflammatory cells were replaced by fibrous tissue.

There is a considerable difference of opinion in regard to what are the characteristic changes in the interlobular fibrous septa. Christian did not describe them. Bailey's[11] view, generally accepted by American investigators, is that "a feature of panniculitis to be emphasized is the tendency for the interlobular connective tissue septa to retain the same width throughout. Edema, necrosis and infiltration may be present but extensive fibrosis, extending from the point where the larger vessels lie, is usually conspicuous by its absence. Thus it seems that the changes occur mainly as a result of lipophagic cells around the smaller blood vessels within the fat lobule." Allen[6] states that the lesion in its typical form is characterized by infiltration of the fat lobules themselves rather than the septa. Baumgartner and Riva[1] describe inflammation and thickening of the connective tissue septa and note also an increase of the intralobular connective tissue. Septal immunity, emphasized by American observers, is an indefinite term that appears to mean absence of fibrosis in the perilobular areas rather than freedom of the septa from infiltration.

The condition of the blood vessels in the nodule is of prime interest for it would seem to furnish a clue to the pathogenesis of the lesion. Christian[3] noted that the blood vessels were usually normal. A few showed periarteritis and rarely endarteritis with proliferation of the endothelial cells. Bailey[11] described obliteration of larger blood vessels and also noted in his third case obliteration of vessels within the fibrous septa. Cummins and Lever[12] in both of their cases described lamellation of the walls of the veins and subendothelial edema. Arnold[9] noted extensive arteriolitis with thrombus formation and recanalization. Larkin[8] noted small vessels surrounded by macrophages, lymphocytes and plasma cells. Zee[10] described infiltration of the vessel walls by inflammatory cells and small hemorrhages into the adipose tissue. Friedman[5] noted proliferation of the adventitia of vessels within the lesion. Shaffer[13] has offered evidence, however, against primary vascular involvement

for in his patient there were widespread changes in the panniculus with softening and rupture of the nodules, but biopsy of a very early lesion showed only minimal perivascular inflammation.

Five patients with Weber-Christian disease have been autopsied. Kritzler's[7] patient showed no striking changes in the internal fat deposits. A fatty liver with widespread central necrosis was found and the spleen was enlarged. Fat emboli were present in the lungs and many of the cells of the adrenal cortex had undergone hydropic degeneration. The case of Spain and Foley[4] ran a course of eight days, terminating in uremia. Autopsy revealed chronic glomerulonephritis and Weber-Christian disease. In addition to subcutaneous fat necrosis there was necrosis of the pancreatic adipose tissue and of areas in the mesenteric, omental and peritracheal fat. Fatty changes were present in the liver. It has been doubted that Friedman's[5] case should be considered one of Weber-Christian disease because the patient died of staphylococcus septicemia. The duration of the disease was five years with multiple subcutaneous nodules appearing during that time. That coagulase-positive Staphylococcus aureus was obtained from a terminal blood culture does not appear to us to influence the original diagnosis of Weber-Christian disease. It is impossible, however, to separate the postmortem findings due to the panniculitis from those due to terminal septicemia. The same is generally true of Ungar's[14] case although he offered much less clinical evidence to substantiate a diagnosis of Weber-Christian disease. The latest autopsied case is that of Mostofi and Engleman[15] whose patient died in a convulsive seizure seven months after onset of the disease. The liver showed fatty changes, especially in the peripheral cells; the midzonal and central areas were the sites of necrosis and hemorrhage; early proliferation of the bile ducts was noted. The pancreas revealed fatty and hydropic degeneration of the acinar cells. The peripancreatic and intralobar fat was infiltrated with plasma cells, lymphocytes and phagocytes. The inflammatory reaction was closely related to the small arteries and veins. There also was considerable involvement of the peripelvic and peri-adrenal fat and of the epicardium. Widespread reticuloendothelial hyperplasia was noted.

The most constant postmortem findings are non-specific fatty infiltration and necrosis in the liver. The changes in the internal fat deposits mimic those noted in the subcutaneous adipose tissue.

The cases reported since 1944 are summarized in Table III.

CASE REPORTS

CASE 1. J. H., a sixty-three year old Belgian male, entered the hospital February 19, 1946, complaining of joint pains, fever and subcutaneous nodules of two weeks' duration.

At the age of seventeen the patient had an attack of polyarthritis that confined him to bed for six months. He was well until the age of thirty-three when he developed polyarthritis and subcutaneous nodules. That illness differed from the present only in that it was much less severe and less abrupt in its onset. Symptoms (at that time) continued intermittently for three years with exacerbations lasting for about a month, followed by remissions of from two to three months. From the age of thirty-six to the onset of the present illness he had been free from any similar complaints. System review revealed only a history of dyspnea on moderate exertion lasting for the past two years.

Physical examination revealed that the patient was an elderly white male who appeared both acutely and chronically ill. The temperature was 102.4°F., pulse 96 and respiration 22. The skin was warm, loose and dry, with evidence of moderate weight loss. The pharynx was acutely inflamed. The heart was slightly enlarged to percussion and the rhythm was regular with rare premature contractions. The heart sounds were of good quality with a blowing systolic murmur (grade III) at the apex. Blood pressure was 135/85. Both elbows were swollen, tender, red and hot. The shoulders and knees were tender and motion was limited because of pain. There were two raised, red, firm, nontender nodules in the subcutaneous tissue apparently attached to the epidermis. The larger nodule (5 by 6 cm.) was on the posterior

TABLE III

Author	Age	Sex	Duration	Site	Temperature	White Blood Cells	Therapy	Findings
Kritzler*	34 yr.	F	29 mo.	Thighs; buttocks; arms	101–104°F.	?	?	Autopsy: Non-suppurative exudate in panniculus; collapse of many fat cells; necrosis of the exudate; lipophagocytosis and entry into the adipose cells of wandering phagocytes and lymphocytes, both in the exudate and within the adipose cells; no changes in internal fat deposits; spleen enlarged; liver fatty with widespread necrosis mostly centrally located; fat emboli in lungs; hydropic degeneration of adrenal cortical cells
Larkin	23 mo.	M	6 mo.	Thighs; ankles	102°F.	6,000; 54 per cent polymorphonuclears	?	Biopsy: Polymorphous cellular infiltration, many mononuclear phagocytes with vacuolated cytoplasm between the fat cells; small vessels surrounded by macrophages, lymphocytes and plasma cells
Spain and Foley	51 yr.	M	8 days	Arms; legs	99–104°F.	8,500; 85 per cent polymorphonuclears	?	Biopsy: Fat necrosis with surrounding infiltration of lymphocytes, occasional polymorphonuclears and fat-laden macrophages, moderate increase in fibrous tissue adjacent to lesion. Autopsy: Chronic glomerulonephritis; pancreatic fat necrosis; fatty changes in liver; necrotic nodules in mesenteric, omental and pretracheal fat
Ives	53 yr.	M	10 wk	Arms; thighs	101°F.	1,000–2,300; 59 per cent lymphocytes	Sulfathiazole Penicillin	Biopsy: None
Baumgartner and Riva	56 yr.	F	3 episodes in 8 yr.	Whole body except head; hands; feet	99–102°F.	Early, 5,300; 43 per cent lymphocytes; later, 15,000; 87 per cent polymorphonuclears	?	Biopsy: Infiltration of panniculus by lymphocytes, fibroblasts, some plasma cells; later neutrophil, lipophages and giant cells; connective tissue septa thickened and infiltrated
Friedman	23 yr.	F	5 yr.	Legs; thighs; buttocks; breast	103–105.8°F.	1,700–2,500; 42–55 per cent polymorphonuclears	?	Biopsy: Chronic granulomatous inflammation predominantly involving subcutaneous fat lobules; infiltration with round cells and large mononuclears; proliferated lamellae of adventitial cells about some vessels; death due to Staphylococcus aureus, coagulase positive, septicemia
Arnold	27 yr.	F	17 mo.	Thigh; forearm	99°F.	12,100; normal differential	Recovery attributed to sulfapyridine	Biopsy: Arteriolitis with thrombus formation and recanalization; round cell and polymorphonuclear infiltration and fibrous replacement of subcutaneous fat
Zee	23 yr.	M	1 mo.	Abdominal wall; arm; legs; back; trunk	104.0°F.	3,200; 50–75 per cent polymorphonuclears	Sulfadiazine ineffectual; temperature normal after 15 days of penicillin	Biopsy: Epidermis edematous; fascia and adipose tissue hemorrhagic; minimal infiltration about blood vessels and dermal appendages; coagulation necrosis of some fat lobules, others densely infiltrated with mononuclears and neutrophiles; interlobular septum edematous; small round coccoid bodies with the appearance of bacteria found in some areas
Allen	48 yr.	F	?	Thighs	Low grade	?	?	Biopsy: Infiltration of monuclear cells, lymphocytes and histiocytes that select the fat lobules rather than the septa

* This case not summarized by Larkin.

TABLE III (*Continued*)

Author	Age	Sex	Duration	Site	Temperature	White Blood Cells	Therapy	Findings
Ungar	37 yr.	F	9 mo.	Trunk; forearm; thighs	102–104°F.	18,000; moderate shift to the left	Potassium iodide produced flare-up	Biopsy: First, lipogranuloma; second, suppurative inflammation of adipose tissue Autopsy: acute diffuse, suppurative peritonitis due to Streptococcus hemolyticus; relapsing and granulomatous inflammation of adipose tissue throughout the body predominantly in the retroperitoneal space; ulcer of skin due to extension of suppurative panniculitis to arterioles with subsequent thrombosis; thrombosis of pelvic and iliac veins and inferior vena cava
Mostofi and Engleman	38 yr.	M	9 mo.	Arms; legs; thighs; trunk; forehead	101–104°F.	2,600–5,000; 68 per cent polymorphonuclears	Atabrine, quinine, sulfonamides, emetine, penicillin and antimony, ineffectual	Biopsy: Thin and atrophic epidermis; pink-staining material precipitated inside some fat cells; collapse of the cell membrane of a majority of cells; ruptured cells invaded by foamy macrophages, lymphocytes, plasma cells and neutrophils; macrophages containing an occasional ingested lymphocyte and red blood cells seen; inflammatory reaction marked around small-sized vessels Autopsy: Bilateral blood-tinged pleural effusion; liver: fatty changes in peripheral cells, necrosis and hemorrhage in mid-zone and central areas; proliferation of bile ducts; considerable involvement of peripelvic, periadrenal and epicardial fat; widespread reticulo-endothelial hyperplasia

wall of the right thorax while the smaller (2 by 4 cm.) was on the medial aspect of the right knee. There were no other significant physical findings.

Laboratory data revealed the following: Hemoglobin, 15.6 Gm.; red blood cells, 5,120,000; white blood cells, 15,500; segmented forms, 65 per cent; band forms, 11 per cent; lymphocytes, 24 per cent. Urine: specific gravity, 1.012 to 1.015; albumin: trace. Blood chemistry: uric acid, 2.5 mg.; cholesterol, 233 mg.; sedimentation rate, 18 mm. in 25 minutes; cephalin flocculation, 1 plus in 48 hours. Agglutination for typhoid, paratyphoid A and B, typhus and brucella, negative. Blood culture, negative.

X-ray examination showed that soft tissue swelling was present in both elbow joints. Advanced osteo-arthritic changes of the productive type were present in the right knee with earlier changes in the left knee and in both hip joints.

The patient was hospitalized for sixty-seven days. He had recurrent episodes of fever as high as 105.2°F., accompanied by the appearance of subcutaneous nodules, chiefly on the buttocks and lower extremities but also on the trunk and arms. Pain and swelling of the knees, elbows and shoulders accompanied some of the flare-ups. The longest continuous febrile period was eighteen days. Of the numerous nodules that appeared only one became fluctuant and on aspiration yielded 1.5 cc. of thin, yellow, cloudy fluid. No organisms were obtained on smear or culture of this fluid. During the hospital stay there was a slight decrease in hemoglobin and red cells. Leukocytosis persisted without any change in the differential count. The sedimentation rate remained accelerated. As the nodules subsided there was dimpling of the skin and in some spots brownish pigmentation appeared over the site of the nodules.

Two courses of intramuscular penicillin were given, each for a period of four days for a total of one million units. Salicylates were given orally and rectally in large doses. Neither form of therapy seemed to have any influence on the course of the disease.

A specimen was taken from the right buttock, consisting of skin and subcutaneous tissue, and

a biopsy was performed. The epidermis was intact and showed no changes. There was some edema and slight cellular infiltration of the deeper layers of the derma. No changes were noted in the hair follicles, sweat or sebaceous glands. The septa between the fat lobules were edematous and infiltrated with many cells, chiefly large mononuclears with dark-staining nuclei and granular cytoplasm but also with lymphocytes and polynuclears. (Fig. 1.) There was extensive necrosis of fat cells with evidence of fat being phagocytosed. (Fig. 2.) In addition to the cells described previously large mononuclears with pale nuclei (foam cells) and giant cells were present in close approximation to the necrotic fat. Polymorphonuclear leukocytes were more frequent in areas showing severe necrosis. Mild to moderate perivascular infiltration was noted and there were a few small hemorrhages.

CASE II. D. A., a fifty-eight year old white female, was admitted to the hospital complaining of nausea and vomiting of one week's duration, accompanied by constant, moderately severe pain in the right upper quadrant. There was a past history of intolerance to fatty foods and of several attacks of abdominal pain and vomiting that had been attributed to gallbladder disease.

Physical examination showed that the patient was a moderately obese woman; temperature was 106.2°F. and pulse 120. Blood pressure was 160/100. There was moderate tenderness in the right upper quadrant. The examination was otherwise negative.

The outstanding feature of the laboratory studies was failure of the leukocytes to rise above 9,000 cu. mm. although a moderate shift to the left was noted. The blood Kahn was negative. The urine showed a persistent trace of albumin.

A flat plate of the abdomen in the prone and erect positions revealed slight elevation of the right dome of the diaphragm. The heart was moderately enlarged and the lungs showed increased fibrosis in the roots and bases. The gallbladder was not outlined by the administration of oral dye.

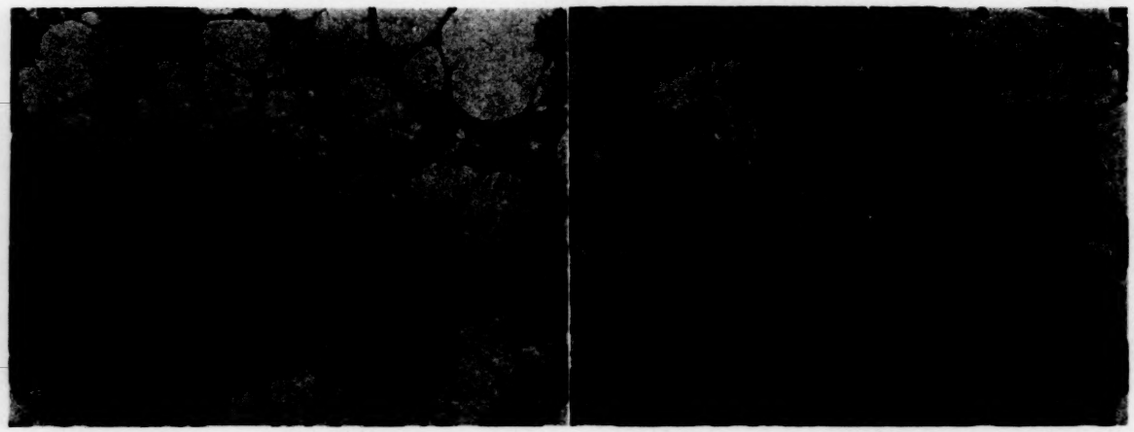
The patient was given 670,000 units of penicillin intramuscularly for a period of seven days. Abdominal signs and symptoms disappeared by the fourth day. By the sixth day the temperature had gradually fallen to 101°F. and remained at that level for eighteen days, during which time subcutaneous nodules appeared on the thighs and arms.

FIG. 1. Case I. Section of panniculus showing marked cellular infiltration of the septa. (× 100.)

A biopsy specimen consisted of subcutaneous tissue. The interlobular fat septa were infiltrated with a great many cells, lymphocytes predominating. (Fig. 3.) Fibroblasts were increased, and there appeared to be proliferation of fibrous tissue in the septa. Fat necrosis was marked. Vacuolated giant and foam cells were present in great numbers. There was a paucity of blood vessels in the areas of fat necrosis and mild perivascular infiltration was the only change noted.

CASE III. R. E. A., a sixty-three year old widow was admitted to the hospital in October 1943, in a stuporous condition. A week prior to admission, while walking, she suddenly lost the power in her legs and fell to the ground without losing consciousness. Since then, she noticed residual weakness in her legs.

The patient had had two previous admissions to this hospital. In 1941 a diaphragmatic hernia that reduced itself when the patient assumed an upright position was demonstrated. In 1943 repair of the diaphragmatic hernia gave her complete relief from periods of abdominal pain, nausea and anorexia. Physical examination revealed evidence of right facial paralysis, a temperature of 101°F. and many scattered subcutaneous nodules of which the patient had been unaware. The nodules were present on the extensor surfaces of the legs, on the medial and lateral aspect of the thighs, over the right elbow and the right arm and left forearm. The nodules were not tender and with the exception of the largest, which appeared to be fluctuant, were



2A 2B

FIG. 2. Case I. A, section of panniculus; extreme fat necrosis. Many large mononuclear cells with foamy cytoplasm present in necrotic areas and between fat cells. (× 100.) B, (× 250).

FIG. 3. Case II. Section of panniculus. Infiltration of the septa with lymphocytes; rare giant cell present. Increase of fibrous tissue in the septa. (× 200.)

firm. The overlying skin was reddened. The diagnosis at admittance was erythema nodosum.

Laboratory data was as follows: Red blood cells, 4,010,000; hemoglobin, 80 per cent; white blood cells, 13,000; polymorphonuclears, 76 per cent; lymphocytes, 21 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent. Urine: 2 plus albumin and 10 to 12 white blood cells per high powered field.

Fluoroscopic examination of the chest showed enlargement of the left ventricle with moderate dilatation of the descending aorta. There was slight dilatation of the lower end of the esophagus and two small diverticula were found in this area.

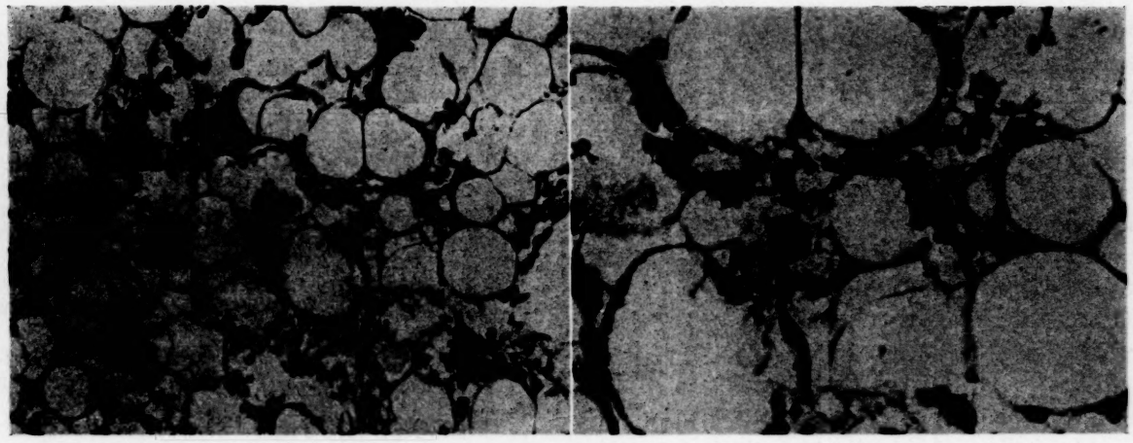
The patients' temperature was 101°F. for the first forty-eight hours; it rose to 104.4°F. on the third day and gradually fell to 100°F. during the next forty-eight hours. For the following six weeks, during which time the nodules gradually disappeared, the temperature fluctuated between 98° and 100.2°F.

The patient was seen in consultation by the Dermatological Service which suggested the possibility of Weber-Christian disease. All symptoms gradually subsided and the patient was discharged on the seventy-second hospital day. No therapy was given.

The biopsy specimen consisted of skin and subcutaneous tissue. No abnormalities were noted in the former. The inflammatory process appeared to be more acute in this specimen than in either of the previous specimens and there was little if any fibroblastic proliferation. The interlobular septa were heavily infiltrated with lymphocytes and polymorphonuclears and these cells were also common in areas of fat necrosis. Multinucleated giant cells were very conspicuous and various stages in the breakdown of fat were demonstrated. (Fig. 4.) The blood vessels showed endothelial proliferation, thickening of the walls and extensive perivascular infiltration with lymphocytes predominating. There were several minute hemorrhages.

Twenty-two months later the patient was re-admitted to one of the surgical services because of a painful mass of one week's duration over the lateral surface of the right knee. She stated that since her previous admission she had had many of these painful areas which persisted for about a month.

Physical examination at this time showed that generally there were no changes since the previous admission. Her temperature was



4A 4B

FIG. 4. Case III. A, section of panniculus. Minimal fibroblastic proliferation. Various stages in the breakdown of fat are present with destruction of cellular boundaries and phagocytosis of fat. (× 100.) B, (× 400).

101.6°F. Over the lateral aspect of the head of the right fibula there was a red, hot mass 3 cm. in diameter in the center of which was a red punctate area with a surrounding zone of erythema about 11 cm. in diameter. The temperature rose to 102.0°F. for twelve days and then in a period of two weeks fell to normal. During this time the mass resolved without fluctuation. The patient was given 6 Gm. of sulfadiazine daily for twelve days.

The patient was again seen in June, 1947 and there had been no recurrence of the nodules. No evidence of atrophy was present.

COMMENT

Relapsing, febrile, nodular, non-suppurative panniculitis is a well defined clinical entity and even in the absence of palpable nodules should be considered as a possible cause of unexplained fever since the early febrile stage, noted in some cases without palpable subcutaneous nodules, may well be due to panniculitis of the internal fat deposits.

No single factor has been advanced to explain the etiology of Weber-Christian disease. Weber[16] doubts that the condition can be considered a pathologic entity. His case and two of Bailey's[11] were manifestly due to the administration of iodides. Ungar's[14] patient had a flare-up following potassium iodide. Weber[16] states that iodides are capable of producing the pathologic picture in certain susceptible individuals. Similar pathologic changes have been produced by local application of cold, by subcutaneous injections and by trauma in established cases. In no instance has direct bacterial action been demonstrated as a cause of the lesions. The small coccoid bodies noted by Zee[10] were not identified. The gram-negative rod recovered by Baumgartner and Riva[1] from a nodule produced necrotic hepatitis and lobular hemorrhagic pneumonia in mice but failed to agglutinate with the patient's serum. Ungar[14] believes that failure to destroy the septum is against direct bacterial invasion.

It appears to us that the changes in the panniculus are secondary to disturbance in the vascular supply to the tissue. This seems to be the only manner in which the widely scattered localization of the inflammation can be explained. The incidence of the lesions on the extremities would seem to be due to the susceptibility of these parts to accidental trauma and to the predilection for vascular lesions to develop on dependent parts. We believe that the reaction in the adipose tissue is due to small areas of ischemia secondary to thrombosis or endarteritis in the smaller vessels, with subsequent death of the fat cells and ingestion of fat by macrophages and mononuclear elements. This explanation would seem to be excluded by the report of Shaffer[13] in whose patient no changes were found in the

blood vessels. That case, however, is not typical of Weber-Christian disease, in that most of the lesions went on to liquefaction, a termination rare in relapsing, febrile, nodular, non-suppurative panniculitis.

The association of severe muscular and joint pain in our first patient with concurrent attacks of panniculitis brings to mind a question by Weber and Gray.[17] "It is a question whether there may not be minor (incomplete) forms of dermatomyositis in which (in the absence of direct examination) the muscles appear to be not or only very slightly affected, and in which consequently a diagnosis of multiple relapsing panniculitis has to be made."

Meakins[18] also states that where fibrositis, panniculitis and myositis begin and end, or whether they are all part of a local lesion, is difficult to determine. These are important points for further investigation for we have been able to find in the literature only a single description of muscle tissue taken in conjunction with the panniculus at biopsy. Conversely, in Weber and Gray's[17] case of polydermatomyositis no mention is made of histologic change in muscle while extensively illustrated descriptions of the changes in the panniculus, considered classical of Weber-Christian disease, are given.

Whether Weber-Christian disease is limited to the panniculus remains to be demonstrated by more extensive biopsy and microscopic study.

SUMMARY

1. The literature on Weber-Christian disease is reviewed.

2. Three additional cases are reported.

3. A vascular disturbance is suggested as a cause of the reaction in the panniculus.

4. A relationship of relapsing, febrile, nodular, non-suppurative panniculitis to dermatomyositis is suggested.

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Serial biopsy studies on patients with pellagra in South Africa offer convincing evidence that fatty liver is the earliest observable lesion of a series of changes which eventually progress to Laennec cirrhosis.[2]

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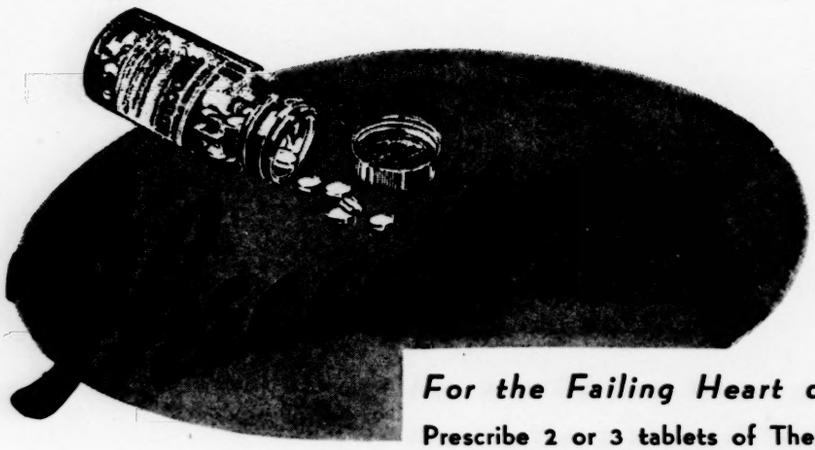

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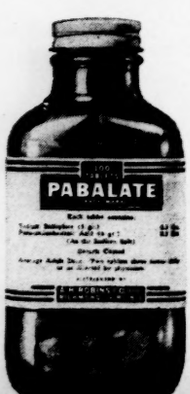

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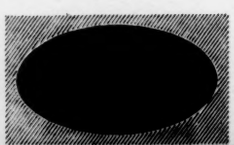

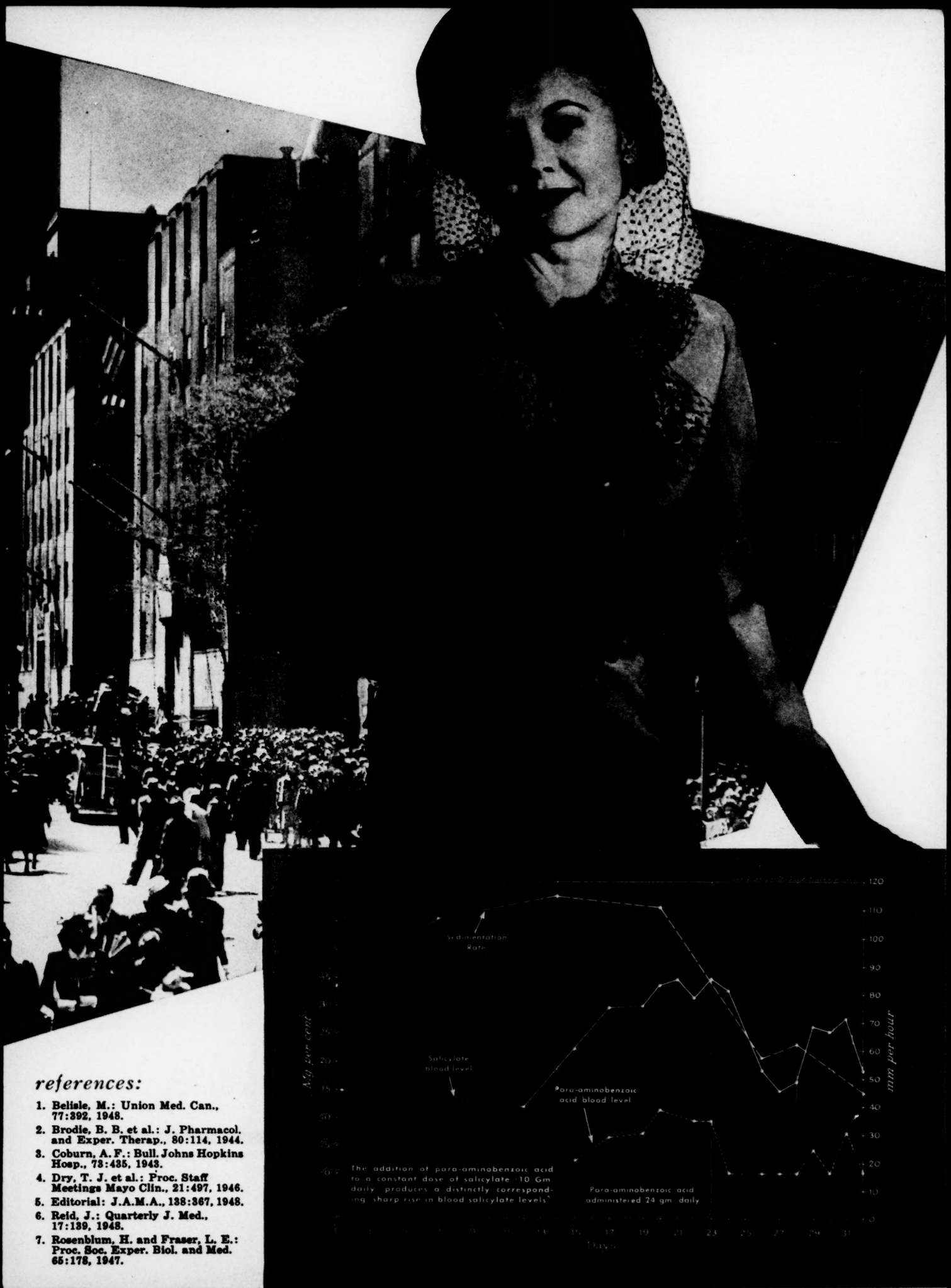

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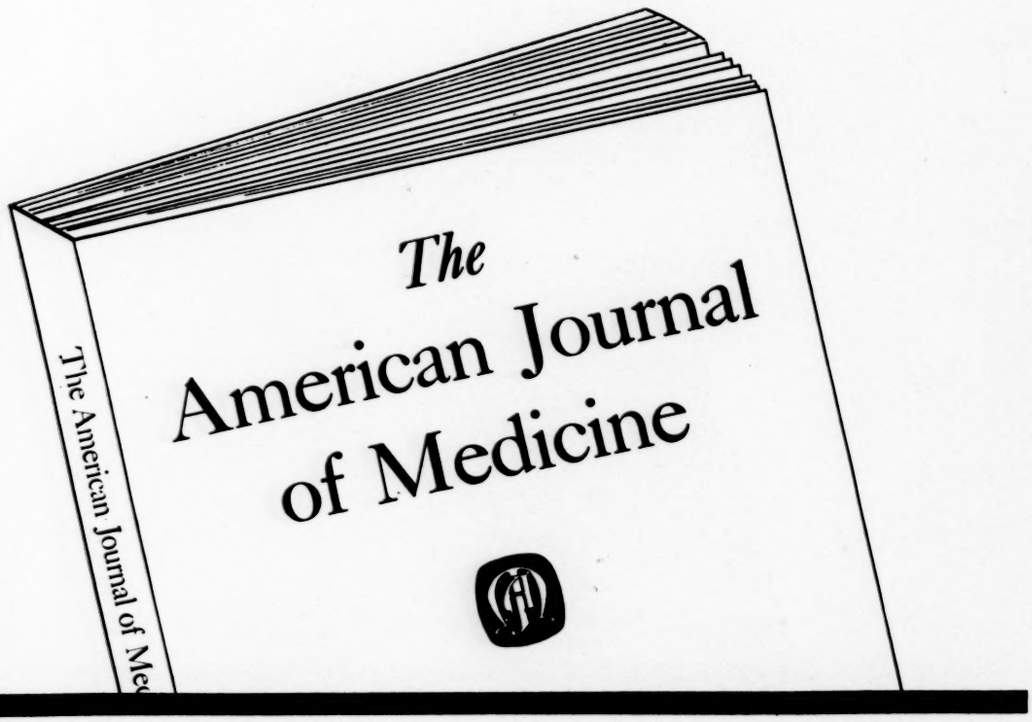

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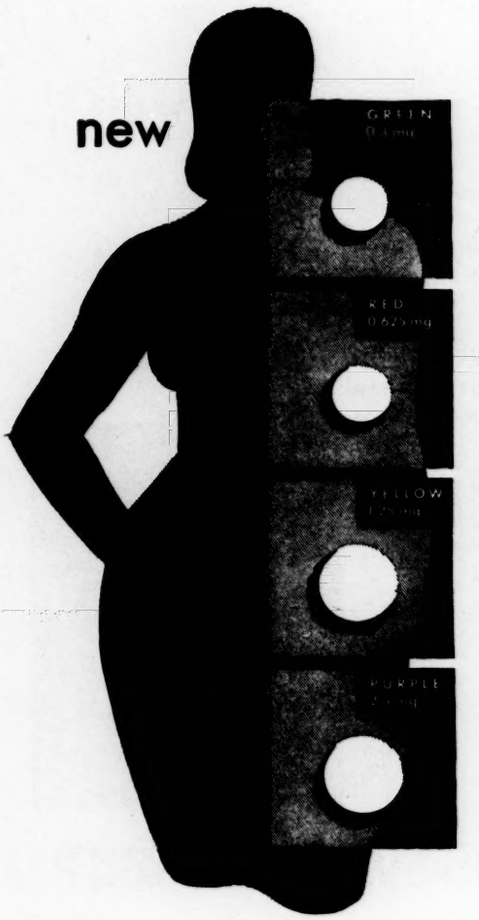

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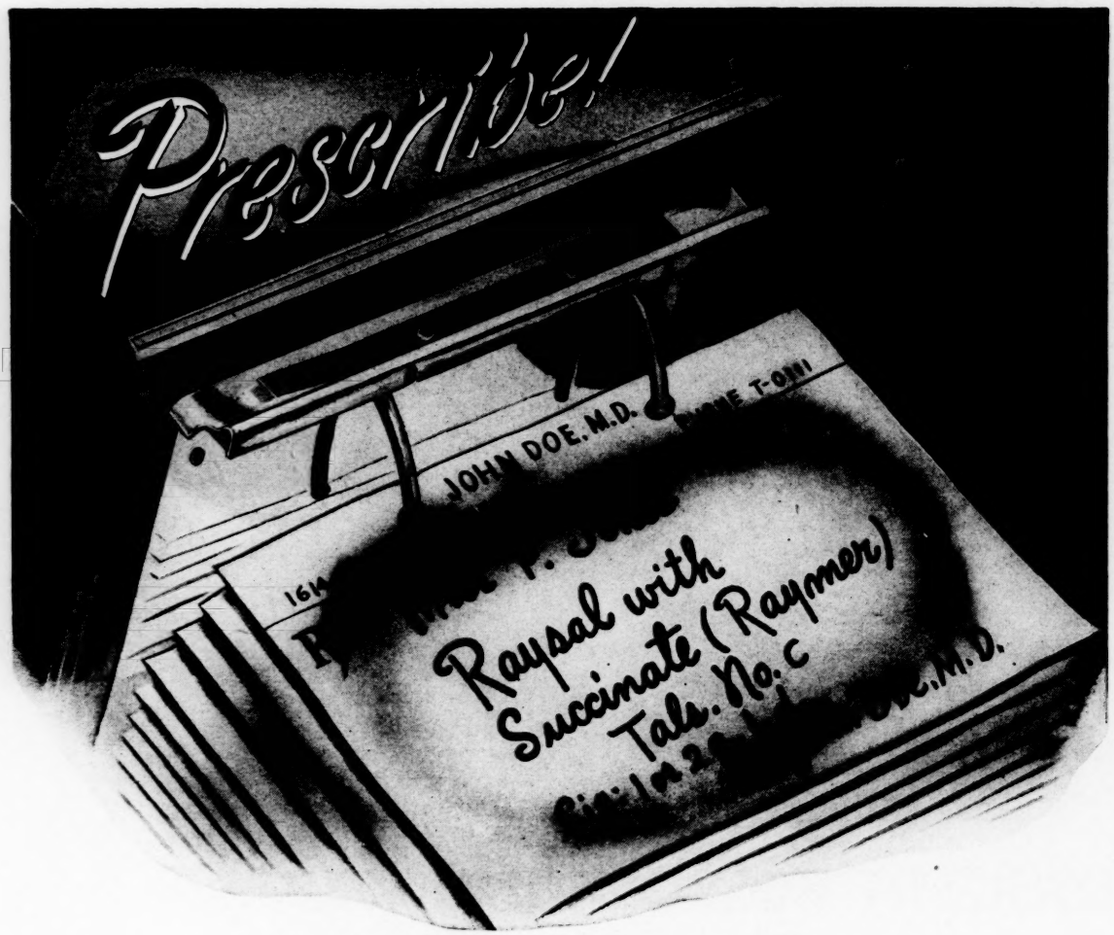

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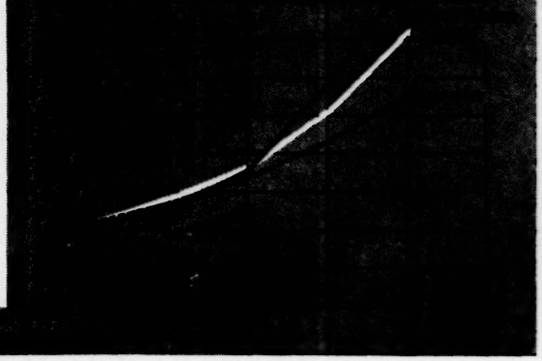

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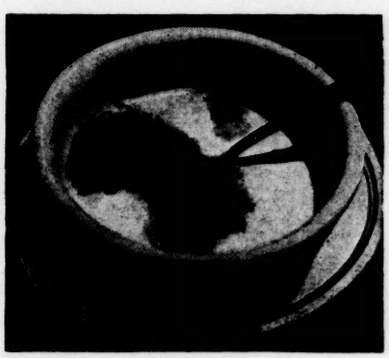

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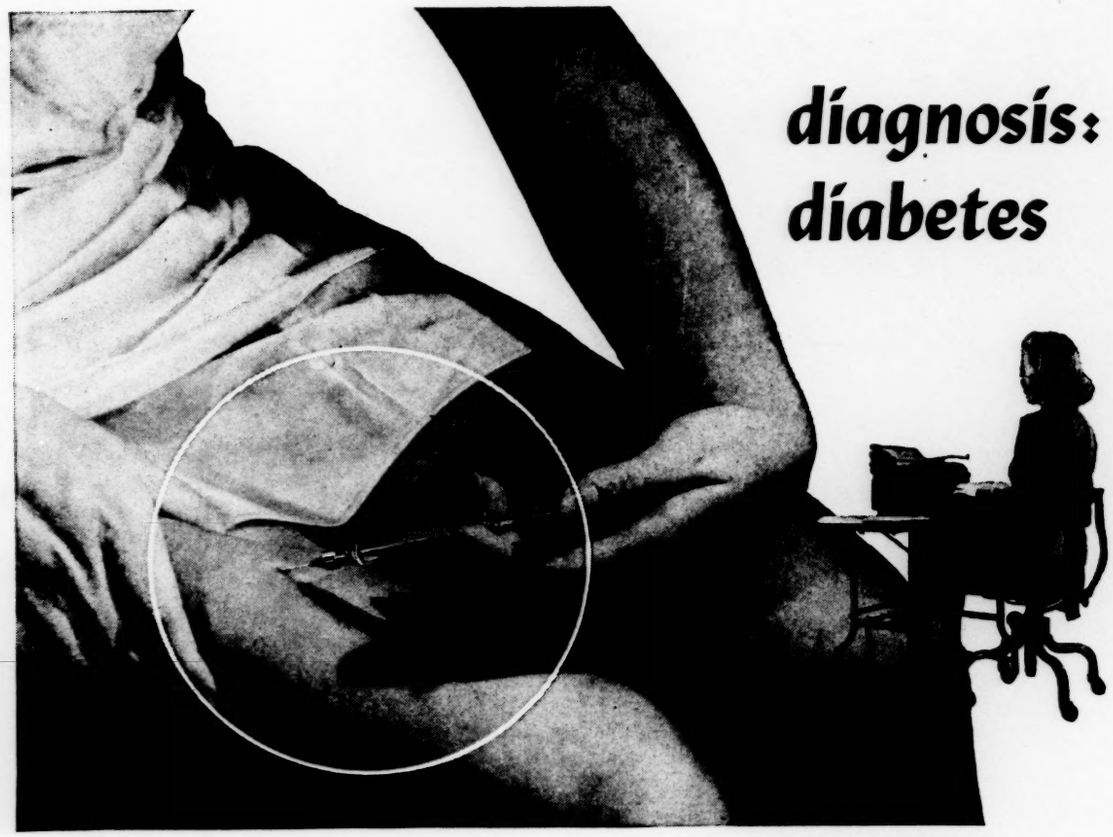

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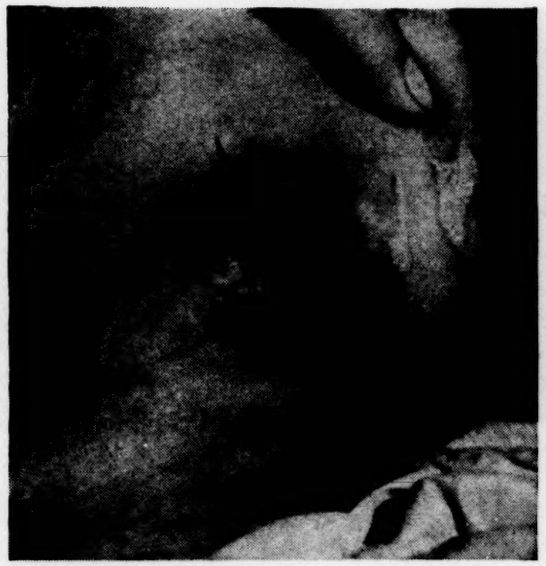

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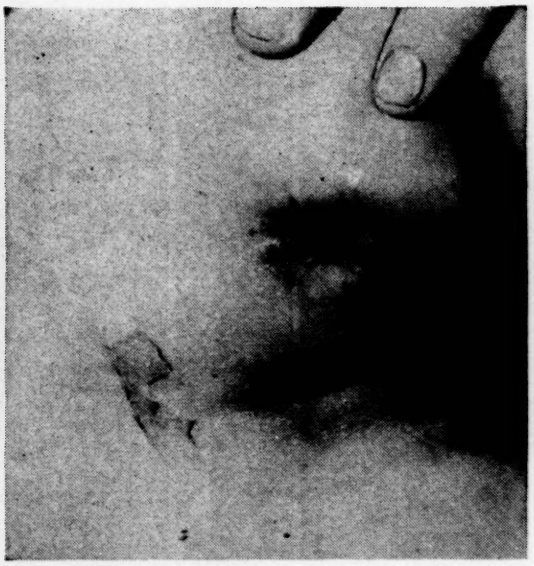

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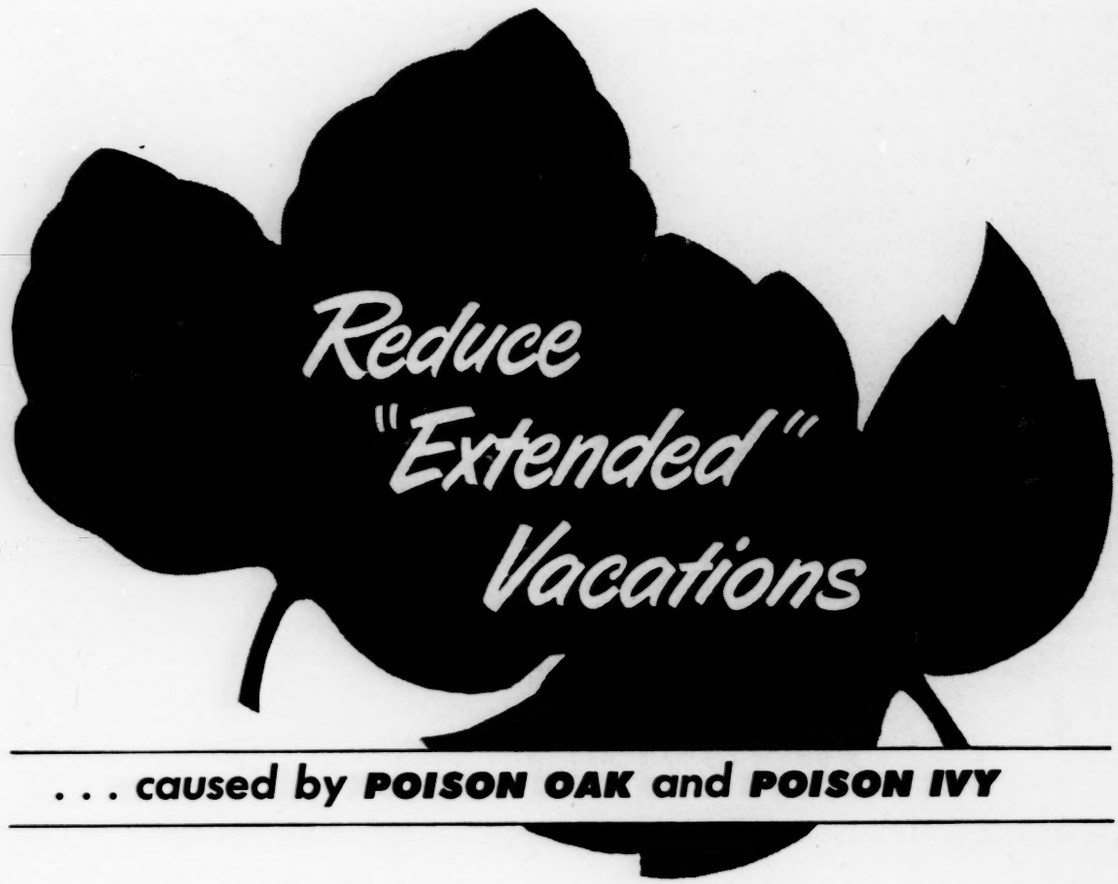

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